Transition metal triflates catalyzed Synthesis of 1-(2-methyl-1, 5-diphenyl-1H-pyrrol-3-yl) ethanone Analogous and Study of Their Antimicrobial activity

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ABSTRACT:

The investigation of new class antibacterial agent of a series 1-(2-methyl-1,5-diphenyl-1H-pyrrol-3-yl)ethanone derivatives (4a–4i) were success fully prepared from phenacyl bromide , substituted aromatic amine and Aetylacetone in the presence of transition metal triflates such as $Cu(OTf)_2$ employed in ethanol under at 70^0C. The designed compounds were examined by advanced spectroscopic data such as ^1HNMR, $^{13}CNMR$ and LCMS and elemental analysis. The protocol has been used because of its excellent yield, short reaction time, mild reaction conditions, and straightforward workup process. 84–92% yields of the synthetic derivatives were obtained. In additionally newly synthesized derivatives were evaluated for their antibacterial activity.

KEYWORDS:

Phenacyl Bromide; Aetylacetone; substituted aromatic amines, $Cu(OTf)_2$; 1-(2-methyl-1, 5- di phenyl- 1H-pyrrol-3-yl),ethanone. Antimicrobial activity

1. INTRODUCTION:

The convergent synthetic reactions known as multicomponent reactions (MCRs) occur when three or more starting materials react to produce a product in which all or most of the atoms contribute to the final product[1,2]. A one-pot synthesis is a method used in chemistry to increase a chemical reaction's efficiency by subjecting a reactant to multiple chemical reactions in a single reactor. Several heterocyclic moieties are very useful and essential for human life, so, many recent reports have confirmed that heterocyclic compound could exhibit numerous biological activities [1-4]. he organic five-membered heterocyclic molecules that make up Pyrrole derivatives and analogues have a complex and intriguing chemistry. The bile pigment contains Pyrrole and its derivatives, as do porphyria and porphyria analogues such bacteriochlorine, chlorine, chlorophylls, cytochromes, hemoglobin, and vitamin B12 (1). Pyrrole is also present in bioactive natural products.

A nitrogen atom is one of the five members of the heterocyclic aromatic structure known as Pyrrole. Because of the lone pair on the nitrogen, which adds to the structure's aromaticity, Pyrrole is the weakest base. Interesting pharmacological characteristics of Pyrrole and its analogues include Biological activity [5-8], Potential HIV-1 [13], luminescence Activity [14[, antifungal agents [15,16], Inflammatory[17], Anticancer activity[18], ,Antitubercular activity [19], Antiglaucomaactivity [20], Antioxidant activity [21], Antileukemicactivity [22], Antitumor activity [23], antibacterial activity [24], antimicrobial Activity [25, 26]

Lately, there has been a renewed interest in doing research without the use of solvents, with a greater focus on developing the principles of green chemistry that are based on reactions .Because of the direct concern for environmental hazards, we specifically try to avoid the use of highly toxic reagents and chlorinated non-polar solvents, such as carbon tetrachloride, dichloromethane, and chloroform. The use of ethanol or an aqueous medium is predominant in organic synthesis and organic reactions, which has drawn more attention to the synthesis process due to atom economy and environmental concerns .Significant research awareness has grown in this area to explore and further develop organic reactions in aqueous media.

One of the main issues and the driving force behind the development of a new class of antimicrobial medicines with stronger activity than already employed treatments is the spontaneous development of resistance by bacterial and fungal stains towards powerful antimicrobial substances. The safest and most readily available solvent is the analgueous Pyrrole; a heterocyclic compound made of phenacyl bromide, acetyl acetone, and substituted aryl amine. It has concentrated on becoming a promoter for synthetic derivatives in a variety of organic processes. It is a very soluble organic base that functions as a nucleophile. Our research efforts to create ecologically favorable reactions will continue.

In order to create 1-(2-methyl-1,5-diphenyl-1H-pyrrol-3-yl)ethanone derivatives, we would like to present a straightforward, effective, useful, and universal one-pot synthesis multi-component reaction. This is achieved by reacting substituted phenacyl bromide and substituted aryl amines with Aetylacetone in an aqueous medium while this solvent is present. It has concentrated on becoming a promoter for synthetic derivatives in a variety of organic processes. It is a very soluble organic base that functions as a nucleophile. As seen in (Scheme-1), we are continuing our research to develop ecologically friendly reactions and investigate the antibacterial activity.

2. MATERIALS AND METHODS:

2.1. Experimental:

All reagents and starting materials were purchased from Merck commercial suppliers and used without any further purification before use. All reactions and the purity of the titled derivatives were

examined by thin-layer chromatography (TLC) using aluminum plates coated with silica gel F254 plates (Merck) using ethyl acetate and n-hexane(5:5) as eluents. All the compounds were evaluated by ^{1}H NMR , ^{13}CNMR and mass spectrometer. ^{1}H NMR spectra were recorded on a Bruker AVANCE 400 MHz and ^{13}C NMR spectra were recorded at 100 MHz The chemical shift were recorded in parts per million (ppm) with TMS as internal reference. Mass spectra were recorded on mass spectrometer using Argon/Xenon (6 kV,mB) gas. Column chromatography was performed on silica gel (Merck). Anhydrous sodium sulfate was used as a drying agent for the organic phase.

2.2. General Procedure

A mixture of phenacyl bromide (10mmol), acetyl acetone (10mmol), substituted aomatic amine (10mmol) and $Cu(TOf)_2$ catalyst(5mmol%) was stirred in 25ml ethanol at 70°C for 6hrs the appropriated time. After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine solution. The organic layer was concentrated under vacuum and the resulting product was directly charged on a silica gel (Merck, 200 meshes) column and eluted with a mixture of ethyl acetate/n-hexane (5:5) to afford the corresponding pure product. All the products were characterized by mass and NMR spectroscopy.

Characterizationsof1-(2-methyl-1,5-diphenyl-1H-pyrrol-3-yl)ethanone derivatives :

2.2.1).1-(2-methyl-1,5-diphenyl-1H-pyrrol-3-yl)ethanone(4a):

Yellowsolid;M.p-154-156^{0}CYeild-85%;^{1}HNMR(400MHz,$CDCl_3$)δppm:7.975-7.365(m,10H,Ar-H), 6.114(s,1H,pyrrole),1.587(s,3H,CH_3),0.965(s,3H,CH_3),^{13}CNMR(100MHz,$CDCl_3$)δppm:193.28,141. 47, 134.78, 131.74, 129.15, 128.97, 128.15, 127.74, 126.47, 125.56, 124.80, 121.46, 118.12, 108.52, 28.95,13.88.LCMS (m/z):275.71(M^+); Molecular formula: $C_{19}H_{17}NO$. Elemental analysis: calculated:C-82.88, H-6.22, N-5.09, Obtained: C-82.81, H-6.21, N-5.18.

2.2.2).1-(1-(4-hydroxyphenyl)-2-methyl-5-phenyl-1H-pyrrol-3-yl)ethanone (4b):

Yellowpowderl;M.p-169-171^{0}C;Yeild-89%.^{1}HNMR(400MHz,$CDCl_3$)δppm:9.525(s,1H,-OH),7.874-7.397(m,7H,Ar-H),6.211(s,1H,Pyrrolering),2.047(s,3H,CH_3),1.596(s,3H,CH_3);^{13}CNMR(100MHz, CDCl3)δppm190.54,143.37, 138.64, 134.05, 129.54, 128.77,127.35,126.44, 125.04, 122.82, 121.75, 119.57, 110.81, 28.95, 13.78: LCMS(m/z)=292.11[M+H]; Molecularformule: $C_{19}H_{17}NO_2$. Elemental analysis: Calculated: C-78.33H-5.88, N-4.81, Obtained: C-78.25,H-5.87,N-4.96.

2.2.3.1-(1-(4-methoxyphenyl)-2-methyl-5-phenyl-1H-pyrol-3-yl)ethanone(4c):

Paleyellowsolid;M.p-174-176^{0}C;Yeil-92%;^{1}HNMR(400MHz,$CDCl_3$)δppm:7.901-7.425 (m, 7H,Ar-H),7.215-7.097(m,2H,Ar-H),6.258(s,1H,pyrrolering),3.784(s,3H,OCH_3),1.662(s,3H,CH_3),0.961(s,

3H, CH_3); ^{13}CNMR(100MHz,$CDCl_3$)δppm:193.51,137.78,136.16, 131.07, 129. 65, 128.74, 128.03, 126.75, 124.76, 121.15, 120.24, 112.97, 54.25, 29.44, 14.18: LCMS (m/z):305.17[M^+]; Molecularformule: $C_{20}H_{19}NO_2$.ElementalAnalaysis: calculated: C-78.61, H-6.28, N-4.61, Obtained: C-78.54, H-6.26, N-4.68.

2.2.4.1-(1-(4-(dimethylamino)phenyl)-2-methyl-5-phenyl-1H-pyrrol-3-yl)ethan-1-one(4d)

Yellowoil;M.p-175-176^{0}C;Yeild-84%;^{1}HNMR(400MHz,$CDCl_3$)δppm:9.784-7.382(m,9HAr-H), 6.258(s,1H,pyrole),2.458(s,6H,$(CH_3)_2$),1.694(s,3H,CH_3),0.988(s,3H,CH_3);^{13}CNMR(100MHz, $CDCl_3$) δppm:191.78,142.56,138.91,134.32,129.84,128.79,128.15,127.57,125.98,1220.09,121.98,119.87, 40. 38,30.25,14.98,:LCMS(m/z)-319.51[M+H];Molecularformule:$C_{21}H_{22}N_2O$;Elementalanalysis: calculated:C-79.21,H-6.96,N-8.80,Obtained:C-79.15,H-6.94, N-8.88.

2.2.4)1-(1-(4-Chlorophenyl)-2-methyl-5-phenyl-1H-pyrole-3-yl) ethanone(4e):

Yellowsolid;M.p-188-190^{0}C;Yeild-87%;^{1}HNMR(400MHz,$CDCl_3$)δppm:97.70-7.332(m,9H,Ar-H), 6.110(s,1H,pyrole),1.596(s,3H,CH_3),0.945(s,3H,CH_3);^{13}CNMR(100MHz,$CDCl_3$)δppm:192.78, 141.56,137.91,135.32,129.54,128.79,128.19,127.28,125.57,121.05,120.45,118.64,30.02,14.35 .:LCMS(m/z)=311.58[M+2];Molcularformulae:$C_{19}H_{16}ClNO$.Elementalanalysis:calculated:C-73.60,H-5.21,N-4.52, Obtained:C-73.56,H-5.20,N-4.58.

2.2.5).1-(1-(4-bromo-2-methylphenyl)-2-methyl-5-phenyl-1H-pyrrol-3-yl)ethanone (4f):

Pale red oil ; M.p-197-199^{0}C;Yeild-90%;^{1}HNMR(400MHz,$CDCl_3$):δppm:7.914-7.515(m, 5H,Ar-H), 7.428-7.270(s,2H,Ar-H),7.222(s,1H,Ar-H),6.324(s,1H,pyrrolering),1.675(s,3H,CH_3),1.223(s,3H, CH_3),0.9892(s,3H,CH_3);^{13}CNMR100MHz,$CDCl_3$)δppm:195.09,137.57,134.49,129.56,129.07,128. 78,128.21,127.55,125.74,123.41,120.77,118.64,116.94,109.45,30.14,18.73,12..84;LCMS(m/z)=367.8 7[M+H];Molecularformule:$C_{20}H_{18}BrNO$.:Elementalanalysis:calculated:C-65.23,H-4.93,N-3.80: Obtained: C-65.19, H-4.92, N-3.86.

2.2.6).1-(1-(4-bromophenyl)-2-methyl-5-phenyl-1H-pyrrol-3-yl)ethanone(4g):

Paleredoil;M.p-194-196^{0}C;Yeild-88%;1HNMR(400MHz,CDCl3)δppm:8.012-7.484(m, 9H), 6.190 (s, 1H),1.688(s,3H,CH_3),0.954(s,3H,CH_3);^{13}CNMR(100MHz,$CDCl_3$)δppmppm: 194.40,138.09, 132.95, 130.94,129.24,128.97,128.45,127.65,126.04,124.58,123.48,121.39, 109.58, 29.07, 14.27; Molecular formulae:$C_{19}H_{16}BrNO$;LCMS(m/z)-354.25,[M+1]+;ElementalAnalaysis:calculated:C-64.42,H-4.55, N-3.95,Obtained:C-64.38,H-4.54,N-4.04

2.2.7) 1-(2-metyl-1-(4-Cynophenyl)-5-phenyl-1H-pyrole-3-yl) ethanone (4h):

PaleYellowoil;M.p-200-202^{0}C;Yeild-87%;^{1}HNMR(400MHz,$CDCl_3$)δppm:8.325-8.157(m,2H,Ar-H), 7.811-7.425(m,7H,Ar-H),6.105(s,1H,pyrrolering);1.518(s,3H,CH_3),0.988(s,3H,CH_3),^{13}CNMR(100 MHz,$CDCl_3$)δppm:197.44,145.92,139.45.134.76,129.54,128.74, 128.21, 127.15,125.54, 123.72, 122.04,121.75,118.77,110.62,29.55,15.46;LCMS(m/z):307.25[M+-H);Molecularformule: $C_{20}H_{17}NO$;Elemental Analysis: Calculated: C-70.54, H-4.85, N-7.65, Obtained: C-7.48, H-4.84, N-70.71.

2.2.7) 1-(2-metyl-1-(3-nitrophenyl)-5-phenyl-1H-pyrole-3-yl) ethanone (4i):

BrightYellowoil;M.p-210-212^{0}C;Yeild-82%;^{1}HNMR(400MHz,$CDCl_3$)δppm:8.278-8.129(m,2H,Ar-H),7.879-7.394(m,7H,Ar-H),6.220(s,1H,pyrrolering);1.326(s,3H,CH_3),1.094(s,3H,CH_3),^{13}CNMR (100MHz,$CDCl_3$)δppm:195.27,145.92,137.45.132.76,129.55,128.57,128. 02,127.58,124.24, 123.72 ,120.94,120.07,119.24,111.62,28.74,13.46;.LCMS(m/z):318.77(M+-H);Molecularformule: $C_{20}H_{17}NO_3$: ElementalAnalysis:Calculated:C-71.24, H-5.03, N-8.74, Obtained: C-71.18, H-5.02, N-8.81.

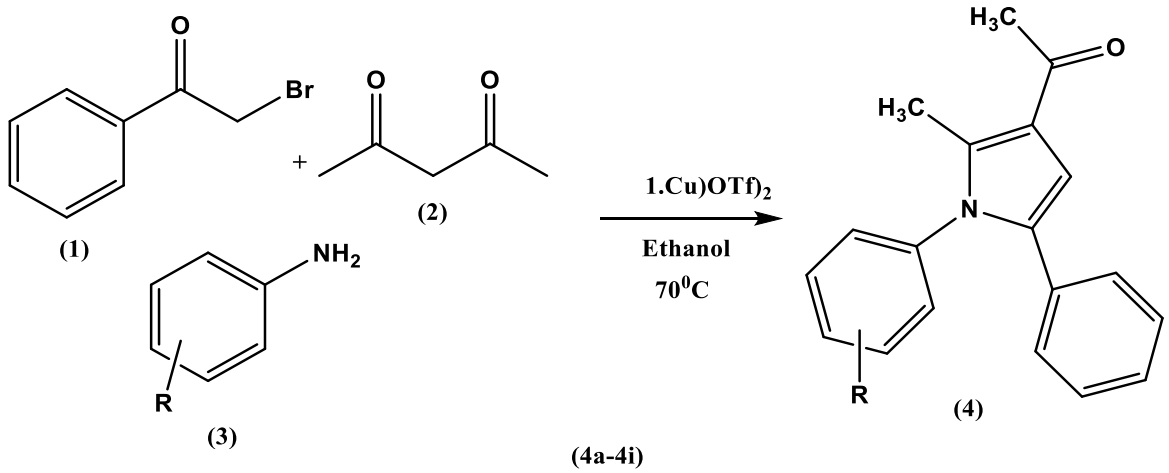
3. BIOLOGICAL EVALUATION:
ANTIBACTERIAL ASSAY:

The antimicrobial activity of 1-(2-methyl-1,5-diphenyl-1H-pyrrol-3-yl)ethanone**(4a-4i)** compounds tested by the diffusion method against various bacteria such as Subtilis , S.aureus, Escherichia coli , P.aeruginosa .For the identification of antibacterial activities, the filter paper disc diffusion method **(14, 15)** was used. Cifraflaxin was used as standard antibiotic for antibacterial activities. Nutrient agar (NA) was used as as basal medium for test bacteria. The agar media were inoculated with 0.5ml of 24h liquid cultures containing 10^7 microorganisms/ml. Diffusion time was 24 h at 25ºC for all bacteria, and incubation time was 36 h at 37ºC. Discs with only DMSOwere used as control. The results of our tested derivatives were presented as the inhibition zones, given in millimeters (mm). The compound that exhibited best antimicrobial activity was further tested by the dilution method.

Antifungal screening:

Antifungal activities of titled compounds were studied (**4a-4i)** towards one human pathogenic and mould fungi. *C. albicans, A. niger* and *A. flavus*. Antifungal activity was assessed by the poisoned food technique in a modified condition**.** Fluconazole was used as standard fungicide. Potato dextrose agar (PDA) was used as basal medium fungi. Glass Petri dishes were sterilized. Sterilized melted PDA medium (45^{0}C) was poured at the rate of 15 ml into each Petridis (90 mm). After solidification of the medium, small portions of the mycelium of each fungus were spread carefully over the center of each PDA plate with the help of sterilized needles. Therefore, each fungus was transferred to number of PDA plates, which were then incubated at (25 ± 2)ºC and ready for use after five days of incubation. Prepared discs of samples were placed gently on solidified agar plates, freshly seeded with the test organisms with sterile forceps. A control disc was placed on the test plates to compare the effect of the test derivatives and to nullify the effect of solvent respectively. Then the plates were kept in refrigerator at 4ºC for 24 h so that the materials had sufficient time to diffuse over a considerable area of the plates. After this, the plates were incubated a 37^{0}C for 72 h. Dimethyl sulphoxide (DMSO) was used as solvent to prepare desired solutions (10 mg/ml) of the derivatives initially and maintain proper control.

4. Results and Discussions:



(4a-4i)

R = H, 4-OH, 4-OCH_3, 4-$N(CH_3)_2$, 4-Cl, 2-CH_3-4-Br,4-Br, 4-CN, 4-NO_2

(Scheme-1)

Chemistry:

The procedure used in this study involved creating new derivatives of the target compounds, Transition metal, such as CuI_2, was first used to improve the synthesis of desired derivatives (4a-4i). This catalyst was imposed during the reaction due to the impact of the reaction rate, developed the percentage of product, and decreased the time factor of the reaction's completion. Along with being commercially available, the workup process was straightforward and easy to handle. The initial reaction of phenacyl bromide (10mmol), phenyl ethylamine (10mmol) and Aetylacetone (10mmol) in ethanol (25ml) at room temperature acquired low yield (40%) of corresponding Pyrrole derivatives even after stirring for extended time (6 hrs). Even after heating the reaction mixture at 70°C for 6 hrs did not increase yield of the derivatives. However, the reaction was forced to completion by the addition of catalytic amount $Cu(OTf)_2$(5mmol %) and desired derivatives of Pyrrole were isolated in high yield (92%). After extensive evaluated of the mole ratio (1mmol, 2mmol, 5mmol %) of $Cu(OTf)_2$, we observed that 5 mol% was suitable for maximum conversion of product. The improved in the mole ratio of $Cu(OTf)_2$ did not improve the yield. Among the solvents like, water, Toluene, Acetonitrile, DCM, Ethanol, methanol, Ethanol appears to acquire the best result. This remarkable development for the catalytic activity of desired catalyst give an incentive for further study of reactions with other substituted aryl amines.

Table-I:- Optimization of the catalyst for synthesis of derivative (4c);

Entry	Catalyst	Time (hrs)	Yield (%)
1	$Cu(OTf)_2$	6	92
2	$CuBr_2$	6	74
3	CuO	6	52
4	$CuSO_4$	6	41

The impact of the solvent in this reaction is the primary goal of the synthesis of titled derivatives. The solvent played a crucial role in the reaction; all of the reactants were fully soluble above, and the starting materials' effects were completed at the proper time, as indicated in **Table II.**

Table-II:- Effect of solvent for synthesis of derivative (4c):

Entry	Catalyst	Time (hrs)	Yield (%)
1	IPA	7	72
2	DMF	7	55
3	CH_3CN	7	76
4	EtOH	7	92

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Another factor in this reaction is the catalyst's quantity; without it, the reaction would not progress. The catalyst was added gradually, and as indicated in **Table III**, the rate of reaction was then raised by a percentage of the yield up to 92% using 30mmole.

Table-III:- Optimization of amount catalyst for synthesis of derivative (4c):

Entry	Loaded catalyst(mmol)	Time (hrs)	Yield (%)
1	1	6	Traces
2	2	6	42
3	3	6	92
4	5	6	92

We have studied the reaction of various substituted aromatic amines and phenacyl bromides to describe the generality of method and the results are summarized in and Substituted aromatic amines possessing electron releasing substituent's like, hydroxyl (entries 4b), methoxy (entries 4c), are smoothly reacted with phenacyl bromides to give desired high yield product. Similarly, halogen substituted aryl amines (entries 4f, 4g) reacted with phenacyl bromides and resulted into expected Pyrrole in good yield. In addition to this, the reaction of electron attracting substituted aryl amines (entries 4h and 4i) with phenacyl bromides and resulted into Pyrrole in moderate yield of expected product.

The measurement of titled compounds estimated by spectral analysis reveals that the proton values of NO_2 and CN group showed at 11.49ppm of the derivative (4b).The –OH protons at 8.93 and 8.87 ppm of the derivatives "4b" and "4c"respectively.The–OCH_3protons showed at3.674ppmofthe derivative "4d".The ^{13}CNMR values of carbonyl carbon showed at 194.27ppm of derivative.

4.2. BIOLOGICAL EVALUATION:

ANTIBACTERIAL ACTIVITIES:

The antibacterial activities of newly synthesized compounds (**4a-4i)** have been assayed against four pathogenic bacteria. Among these pathogens, two were gram-negative and other two were gram-positive. Inhibitory effects of compounds (**4a-4i)** against these organisms are given in **table -IV**. The screening results evidenced that the compounds 4i and 4j did not show any antibacterial activity to the bacteria tested. We observed experimental data and also found that the titled compounds with halogen substituent are the most efficient against Gram-positive bacteria and Gram negative bacteria, particularly against E.coli and P.aeruginosa. The bromoderivatives (4e, 4f, 4g) are of a particular interest since the strong electron-withdrawing effect of chlorine and bromine groups contributes to molecule's biological properties. The isosteric substitution of hydrogen by chlorine, bromine in 1-(2-methyl-1,5-diphenyl-1H-pyrrol-3-yl)ethanone compounds increases the lipophilicity and thus improve the rate of cell penetration, which is a very importance of drug efficiency. The compounds such as 4b, 4c, 4d and 4e exhibited moderate active potential towards every bacteria tested due electron donating groups and low lipophilicity and slowly increases the rate of cell penetration while compound 4a showed very low active potent against *E. coli*, *P. aeruginosa,*

B. subtilis, *S. aureus* due it does not possess electron donating groups and electron withdrawing groups.

Table-I: Antibacterial activity of the Titled derivatives (4a-4i).
Zones of inhibition (mm) of compounds against tested bacterial strains:

Entry	Anti-Bacterial Activity			
	E. coli	***P. aeruginosa***	***B. subtilis***	***S. aureus***
4a	05	08	09	09
4b	16	18	15	16
4c	17	15	18	15
4d	16	17	17	16
4e	12	15	10	12
4f	21	22	19	19
4g	22	20	18	20
4h	11	09	09	11
4i	07	09	05	07
Cifraflaxin	25	25	22	22
DMSO	-	-	-	-

Antifungal activities:

The antifungal activities of designed derivatives **(4a-4i)** have been screened against three pathogens mould fungi. The inhibitory impact of these derivatives was showed against above organisms are given in table –V. The screening results reveals that the compounds 4a, 4i displayed antifungal activities and the derivatives of titled compound such as 4b,4c,4d and 4e exhibited good activity against the three pathogens while the compound 4h,4i showed excellent antifungal activities at high concentration against three pathogens as compared to standard drug viz;Fluconozole. The antifungal activity of the tested compounds indicated that the value of inhibition zone of all the derivatives exhibited lower in *C.albicans* than the *A.niger* and *A flavus*. We identified the results; the compounds possessing hydroxyl group and methoxy group which showed moderate values due partially activate potato molecules. The derivatives “4h and 4i” having electron withdrawing groups which in active nature of biological active potential

Table- V: Antifungal activity of the Titled analogous.

Zones of inhibition (mm) of compounds (4a–4i) against tested fungal strains:

Entry	Anti-Fungal Activity		
	A.Niger	**A. flavus**	**C. albicans**
4a	06	05	06
4b	12	12	13
4c	11	12	11
4d	11	12	14
4e	10	09	09
4f	13	12	10
4g	14	14	13
4h	16	15	16
4i	17	18	18
Fluconazole	20	20	20
DMSO	-	-	-

5. CONCLUSION*:*

The present work describes a rapid, convenient and highly an efficient synthesis of biologically valued 1-(2-methyl-1, 5-diphenyl-1H-pyrrol-3-yl) ethanone analogous is achieved utilizing base by transition metal triflates catalyzed reaction of in ethanol under conventional refluxing conditions. The operational simplicity, good yields short reaction times and use of safe and readily available base catalyst and it a preferred procedure for the synthesis of these compounds. In additionally, the evaluation of antimicrobial activity of the titled derivatives. Antifungal activity of the derivatives bearing electron withdrawing groups displayed more activity than the compound having electron donating group,

6. ACKNOWLEDGEMENTS:

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7. CONFLICT OF INTEREST:

We declare that we have no conflict of interest

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Biological activity [5-8], Potential HIV-1 [13], luminescence Activity [14[, antifungal agents [15,16], Inflammatory[17], Anticancer activity[18], ,Antitubercular activity [19], Antiglaucomaactivity [20], Antioxidant activity [21], Antileukemicactivity [22], Antitumor activity [23], antibacterial activity [24], antimicrobial Activity [25, 26]