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Synthesis, Characterisation and Antimicrobial Studies of Newly Synthesized 2, 4, 5-Trisubstituted-1-H-Imidazole Derivatives From 4-Methoxybenzil.

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Abstract

In this study, new imidazole derivatives were synthesized. The first stage involved the preparation of 4-methoxybenzoin by reacting 4-methoxybezaldehyde with benzaldehyde in presence of sodium cyanide as a catalyst in ethanol .The second stage, involved the synthesized 4-methoxybenzil using conc.nitric acid as an oxidizing agent in presence of glacial acetic acid .Finally the preparation of 2-(Substituted phenyl)-4-(4-methoxyphenyl)-5-phenyl-1H-imidazole was carried out by the condensation between 4-methoxybenzil , substituted benzadehyde and ammonium acetate in glacial acetic acid as a solvent .The synthesized compounds were evaluated for their antimicrobial activity using Gram positive and Gram negative bacteria and found to be more potent antimicrobial drugs .All synthesized compounds were characterized by melting point ,IR ,^{1}HNMR spectral and elemental analysis .The 2-(Substituted phenyl)-4-(4-methoxyphenyl)-5phenyl-1H-imidazoles can act as a template for further development through modification to design more potent biologically active compounds.

Keywords - 4-methoxybenzil, Imidazole derivatives, Antimicrobial activity.

Introduction

Many heterocyclic compounds due to their specific activity are employed in the treatment of many infectious diseases . Imidazole provide one of the most fascinating class of compounds recognized for various pharmacological activities like anti-HIV , anticonvulsant [1] ,HIV-1 protease [2] ,therapeutic agent [3] ,antihistaminic [4] , tranquilizer [5] ,antimuscarinic [6] ,ant arthritis [7] , cardio tonic[8] , and antitumor agents [9] .

Literature survey reveals that several methods have been developed for the synthesis of 2,4,5-triaryl-1H-imidazoles by the three component cyclocondensation of 1,2-diketone , α –hydroxyketone with aldehyde and ammonium acetate which comprises the use of ionic liquids [10] ,alum[11] , Sulphanilic acid [12] ,H_3PO_4 [13] , CAN[14] , I_2[15] .Recently imidazoles have also been prepared by using $InCl_3$ .H_2O[16]. Microwave assisted synthesis of tri and tetra substituted derivatives was also been reported .But during the reaction got sticky solid was formed which indicates that, it is not clear approach [17] .Many of these methods create one more drawback like harsh reaction condition , low yield ,laborious work ,prolong reaction time ,uses of catalyst etc .Due to many drawbacks ,so the development of new non-catalytic method is necessary condition for the synthesis of multi-substituted imidazoles .Encouraged by these

observation, We have synthesized various 2-(Substituted phenyl)-4-(4-methoxyphenyl)-5-phenyl-1H-imidazoles by condensation of 4-methoxybenzil with substituted benzaldehyde, ammonium acetate without use of catalyst and screened them for antimicrobial activity .As a part ongoing efforts towards the synthesized of new substituted imidazoles by 4-methoxybenzil with substituted benzaldehyde ,ammonium acetate without used of catalyst and screened them for antimicrobial activity.

Materials And Methods

Substituted aromatic aldehydes ,anisaldehyde ,benzaldehyde ,sodium cyanide ,ethanol, Conc. nitric acid, ammonium acetate ,glacial acetic acid is required chemicals purchased from S-d fine chemicals. The chemicals were used as received. All the used chemicals were of analytical grade .Melting point were measured in open capillary tube and are uncorrected .IR spectra were recorded in KBr pellets .The ^{1}HNMR was recorded on Bruckner AVANCE 400 MHz spectrometer using TMS as an internal standard .The purity of compounds was checked by TLC on silica gel in solvent system petroleum ether and ethyl acetate (80:20) and the spots were located under iodine vapor as a visualizing agents .

Synthesis

General Procedure for the synthesis of4-Methoxybenzoin: [2-hydroxy-1-(4-methoxyphenyl)-Ethan-1-one]. (C-1) --

To a mixture of 12.3 ml (0.1 mol) 4- methoxybenzaldehyde ,10.6ml(0.1mol) benzaldehyde added 4.9 gm (0.1 mol) sodium cyanide in 20 ml water and refluxed for 4 hours under a water condenser , after which it was cooled under the cold tap water with continuous shaking for 15minutes .Poured the reaction mixture to ice cold water , On keeping it overnight , obtained hard crusts of 4-methoxybenzoin , dried it and re-crystallized from ethanol .

Yield - 52%. M.Pt - 104^{O}C, M.Wt – 242 , Formula – $C_{15}H_{14}O_3$,IR - (KBr cm^{-1}) 3478.50 (O-H) ,3062.86 (Ar C-H) , 2966.75 (C-H Str), 1662.73(C=O) 1600 (Ar C=C) , 1263 .59 (C-O Str). ^{1}H NMR (DMSO)- 3.79 (S ,3H , - OCH_3) , 5.89(S, 1H, C-H) 6.83,(S, 1H, OH) 6.9 to 7.6 (m, 9H aromatic).Elemental analysis: $C_{15}H_{14}O_3$, Calcd – C, 74.38 ; H,5.78 Found**:** C,74.33; H,5.73.

Synthesis of 4-Methoxybenzil: [1- (4- methoxyphenyl) -2-phenyl ethan-1, 2-dione)] (C-2)

Took 6.0 gm 4-Methoxybenzoin dissolved it in 12 ml glacial acetic acid , then added 18 ml Conc. Nitric acid slowly to a reaction mixture (During addition reaction mixture kept in an ice bath) . Refluxed the reaction mixture for 2 hours until the complete evolution of brown gas, stopped , Cooled the reaction mixture and poured to ice cold water with stirring Obtained a solid product, dried it and re-crystallized from ethanol.

Yield- 65%, M.Pt- 63^{O}C, M.Wt -240, Formula –$C_{15}H_{12}O_3$ IR (KBr cm^{-1}) : 3071.27(C-H Ar) , 2991 (C-H ali -OCH_3) , 1676.27(C=O) , 1536.59 (C=C) , 1208.17 (C-O). ^{1}HNMR (DMSO) **:**3.9 (S ,3H, -

OCH_3) , 7.2 (d, 2H) , 7.5 (d , 2H) . 7.96 (S, 1H), 8.0 to 8.6 (m, 4H, arom). Elemental analysis for $C_{15}H_{12}O_3$, Calcd:C,75.00 ;H,4.95 ;Found:C,75.06;H,4.91.

Synthesis of 2-(Substituted phenyl)-4 - (4-methoxyphenyl)-5-phenyl -1H- imidazoles(4a)

A mixture containing 4-Methoxybenzil (0.01mol) , benzaldehyde (0.01mol) , ammonium acetate (0.02mol) was taken in a 100ml round bottom flask was shaken in 15 ml glacial acetic acid , It was refluxed on a water condenser for 6 hours , cooled the reaction mixture and poured into crush ice cold water , kept it for 10 to 20 minutes ,Obtained a solid product was filtered it and recrystallized from ethanol .

Colour–Colourless, Yield-81%, Melting.Pt-209^{O}C,

IR- (KBr cm^{-1}) **:** 3440 (N-H) , 3021 (C-H aro), 2920 (C-H aliph) , 1675 (C=N), 1426 (C=C aro),1092(C-O) .^{1}H NMR (DMSO) , 4.04 (S , 3H ,-OCH_3) , 6.8(d,2H) , 7.0(d,2H) 7.2(d,2H) ,7.3 to 8.1 (m ,8H) , 9.2 (S, 1H , N-H). Elemental analysis for$C_{22}H_{18}N_2O$, Calcd**:** C,80.95; H, 5.57; N,4.32, Found C,80.98; H, 5.52 ; N ,4.28

2- (4-Chlorophenyl) -4 - (4-Methoxyphenyl)-5phenyl -1H- imidazole -(4b) -

Solid , Colour- Yellow , Yield -72 % , M.Pt -242^{O}C ,M.Wt-360.5 .IR (KBr cm^{-1}) 3454cm^{-1}(N-H) ,3054Cm^{-1} (C-H arom) , 2938cm^{-1}(C-H ,-OCH_3) ,1682cm^{-1} (C = N), 1426cm^{-1} (C = C), 1092 cm^{-1} (C-O str), 761(C-Cl) .^{1}HNMR (DMSO) 4.09(S ,3H ,-OCH_3) , 6..9 (d, 2H) ,7.2(d ,2H) , 7.3(d, 2H) ,7.4 to 8.1 (m,7H) , 9.31 (S ,1H ,N-H) . Elemental analysis for $C_{22}H_{17}ON_2Cl$, Calcd: C, 73.23; H; 4.71; N, 7.76; Cl, 9.84; Found: C, 73.20; H, 4.70; N, 7.75; Cl, 9.81.

Results and Discussion

As shown in Fig-1 , 4-Methoxybenzoin was prepared from Anisaldehyde (4-Methoxybenzaldehyde) and benzaldehyde via condensation reaction in ethanol using aq.NaCN as a catalyst under refluxed condition for 4 Hrs obtained a 52% yield of product .The structure was confirmed by IR and ^{1}HNMR spectroscopic method .The IR spectrum of product showed absorption band at 3478.50 cm^{-1} and 1662.73 cm^{-1} attributed to the presence of OH and C=O groups .The ^{1}HNMR spectrum of this compounds showed the presence of CH_3 ,the appearance of multiple peaks in the region of δ 3.79 and δ7.6 corresponding to the presence of aromatic ring system in the molecules .

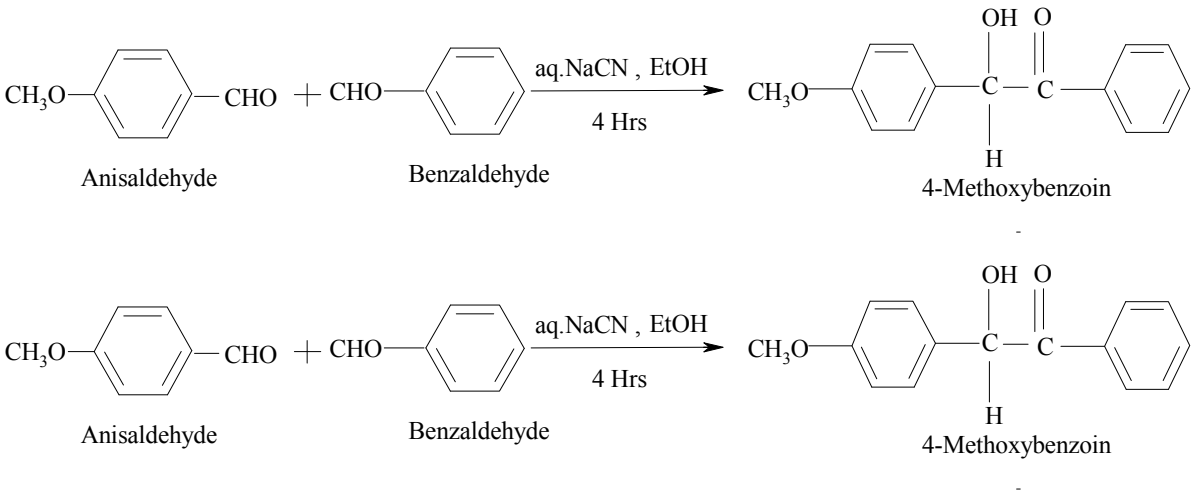


Fig -1 Synthesis of 4-Methoxybenzoin

In fig-2 -4-Methoxybenzil was prepared from 4-Methoxybenzoin in glacial acetic acid using conc. Nitric acid as a oxidizing agents under refluxed condition for 2 hours .The reaction undergoes completion , to give 65% isolated yield of product .The structure was further confirmed by IR and ^{1}HNMR spectroscopic methods .The IR spectrum of product showed absorption band at 1676.27 cm^{-1}attributed to the presence of C=O group .The ^{1}HNMR spectrum of this compound showed the presence of CH_3, at δ 4.04 .The multiple peaks at δ7.3 to 8.1 correspond the presence of proton of aromatic ring .

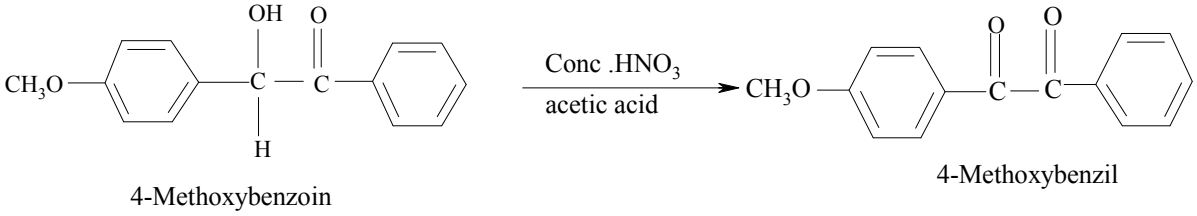


Fig 2 Synthesis of 4-Methoxybenzil

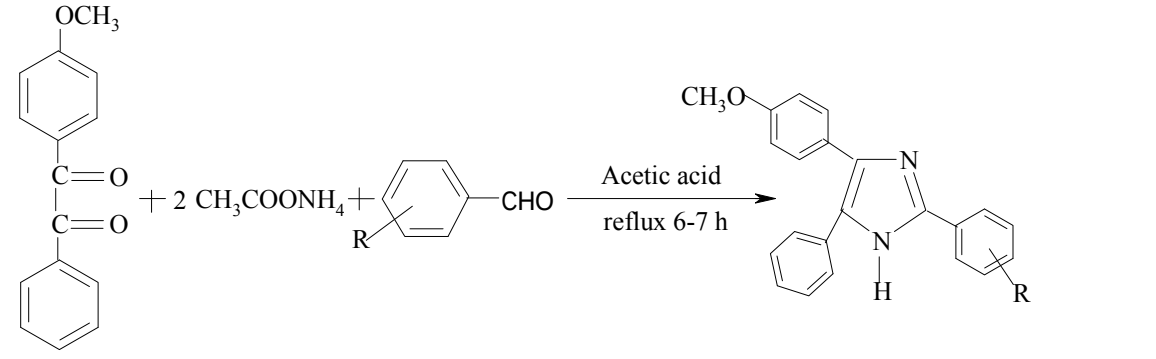


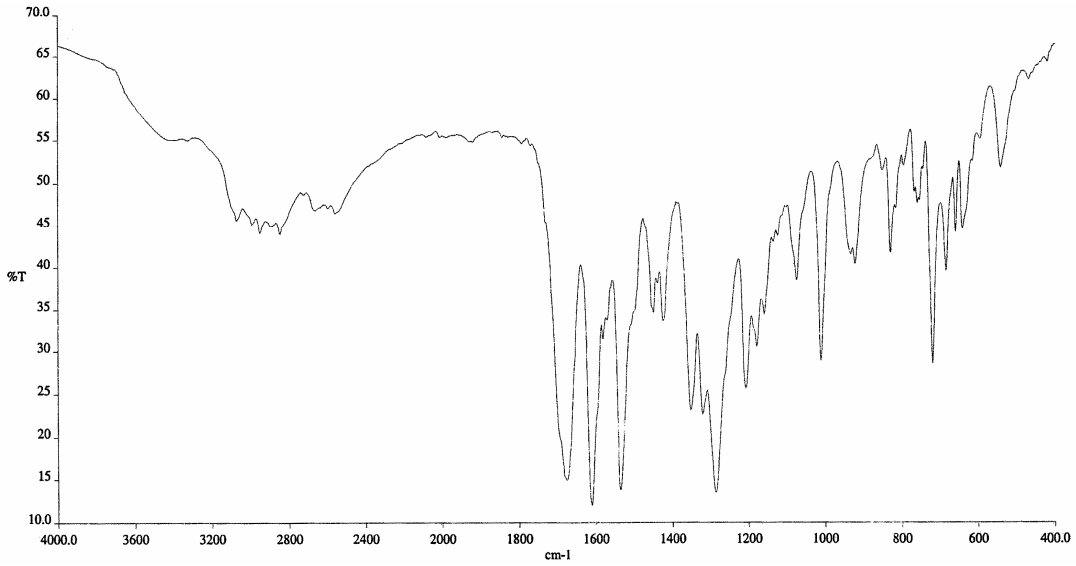
Fig 3 Synthesis of Substituted imidazole

(R- H, Cl, NO_2 , OCH_3 , $N(CH_3)_2$,OH , 3,4,5-$(OCH_3)_3$, -4(OH)-3-(OCH_3))

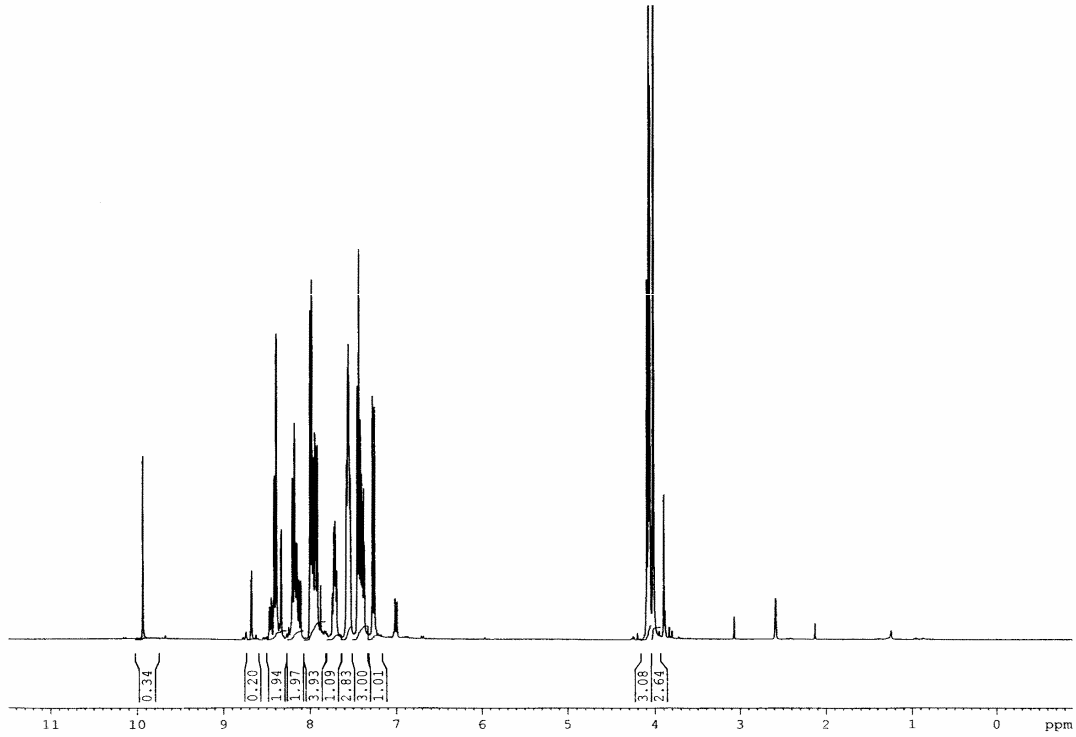
In Fig-3- 2-(Substituted phenyl)-4-(4-methoxyphenyl)-5-phenyl-1H-imidazole was prepared from 4-methoxybenzil ,ammonium acetate ,Substituted benzaldehyde in glacial acetic acid as a solvent ,Obtained 80% yield under reflux condition for 6-7 hours. The present method offered efficient and high yielding process for the condensation of various substituted aromatic aldehydes .This method was found to be very useful to carry out the condensation with high yield (55-81%).It is noteworthy to mention that this synthesis route required simple workup procedures .The imidazole derivatives formation was confirmed by IR,[1] HNMR spectroscopy methods and elemental analysis. The 2-phenyl-4(4-methoxyphenyl)-5-phenyl-1H-imidazole,showed IR absorption band 3440cm^{-1} for N-H , 3021 cm^{-1} for Ar,C-H stretch ,2920 cm^{-1} for C-H ali –OCH_3 ,1675 cm^{-1} for C=N stretching ,1426 cm^{-1} for C=C stretch vibration .The ^{1}HNMR spectrum of this compound was showed the presence of a singlet at δ4.04 due to the presence of CH_3 group and singlet at δ 9.2 for N-H. The formation of imidazole derivatives was further confirmed by physical constant study. The multiple peaks at δ7.3 to 8.1 corresponds the presence of proton of aromatic ring.

Table1: Physical data of the compounds

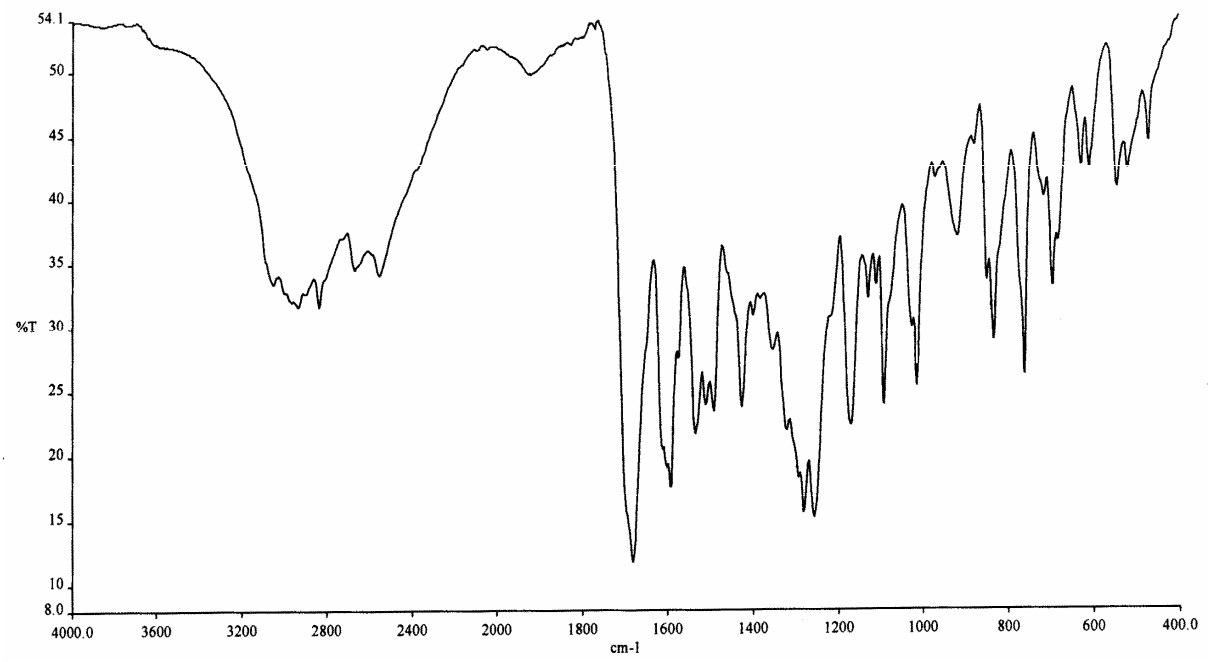
S.No	Entry	R	M.Pt (^{O}C)	M.Wt	Formula
1	**4a**	-H	210	326	$C_{22}H_{18}ON_2$
2	**4b**	-4Cl	242	361.5	$C_{22}H_{17}O_2N_2Cl$
3	**4c**	-4OCH_3	209	356	$C_{23}H_{20}O_2N_2$
4	**4d**	-4NO_2	213	372	$C_{22}H_{18}O_3N_3$
5	**4e**	-2NO_2	178	372	$C_{22}H_{19}O_3N_3$
6	**4f**	-4$N(CH_3)_2$	199	369	$C_{24}H_{23}ON_3$
7	**4g**	-2OH	223	342	$C_{22}H_{18}O_2N_2$
8	**4h**	-4(OH)-3-(OCH_3)	239	372	$C_{23}H_{20}O_3N_2$
9	**4i**	3,4,5-$(OCH_3)_3$	232	416	$C_{25}H_{24}O_4N_2$
10	**4j**	4Cl	180	361.5	$C_{22}H_{17}ON_2Cl$
11	**4k**	- 4(OH)	195	342	$C_{22}H_{18}O_2N_2$
12	**4l**	-3NO_2	188	372	$C_{22}H_{18}O_3N_3$



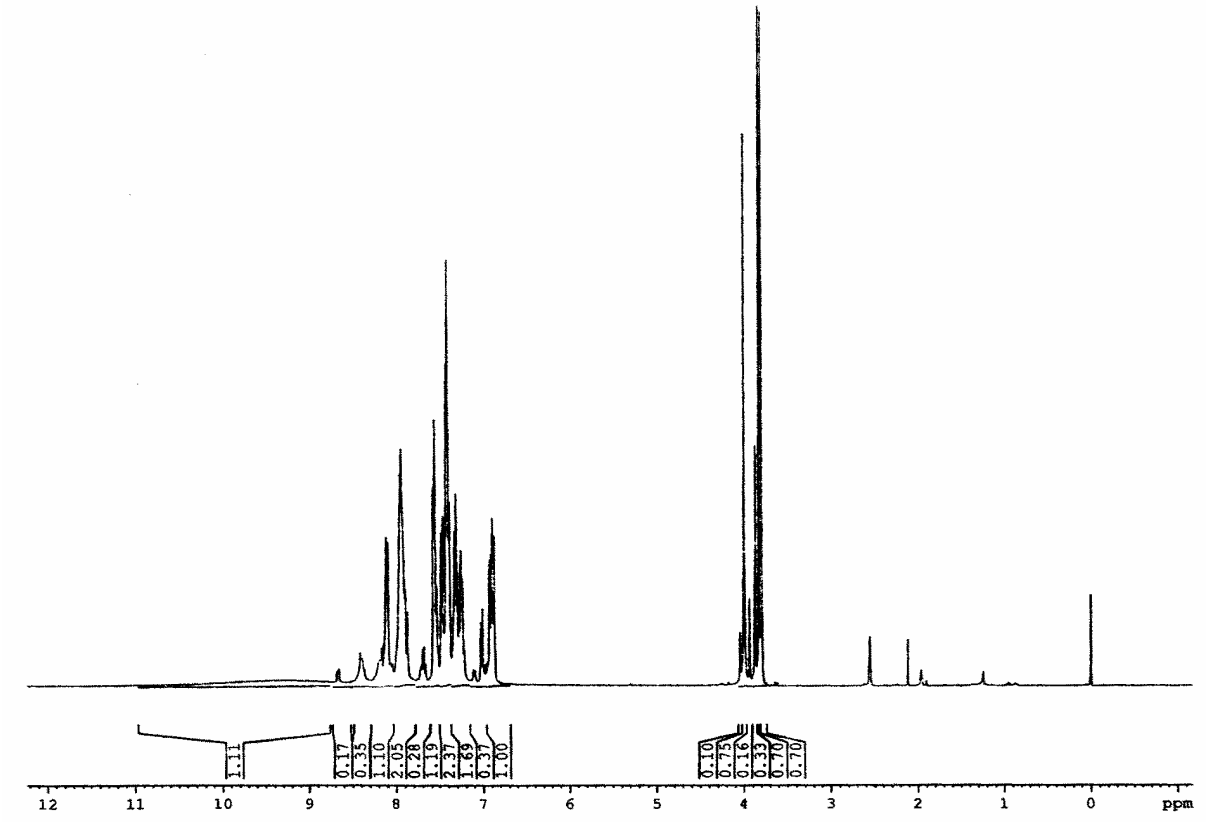
IR Spectra of 4-Methoxybenzil



NMR Spectra of 4-Methoxybenzil



IR-Spectra of 2-(4-Chlorophenyl)-4-(4-Methoxyphenyl)-5-phenyl-1H-imidazole



NMR Spectra of 2-(4-Chlorophenyl)-4-(4-Methoxyphenyl)-5-phenyl-1H-imdazole

Antimicrobial Activity

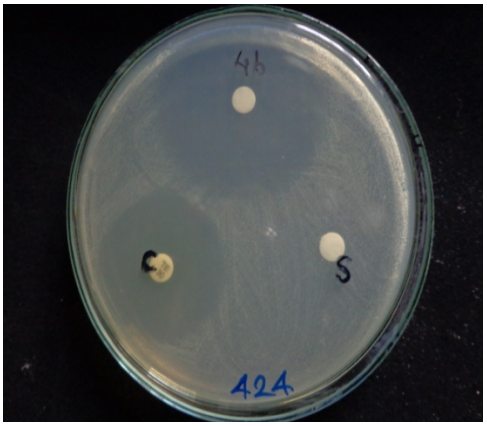
Methods for the determination of antimicrobial activity

The antimicrobial activity of the compounds was carried out by agar plate method .The antimicrobial activity was carried out at a 200 µg/ml in dimethylformamide (DMF) and tetracycline was used as standard .The antibacterial activity was evaluated by 24 hr cultures of ***Klebsiella pneumonia , Escherichia Coli , Staphylococcus aureus , Salmonella typhi , Pseudomonas aeruginosa*** .The medium was sterilized by autoclave at 120^{O}Cfor 30 min ,by pouring the sterile agar into petri-dishes in aseptic condition .The plates were left at room temperate to allow solidification of the media .The 0.1ml of each standardized test organism culture was spread onto agar plates .The disk diffusion method was used for the antibacterial evaluation . After incubation at 37^{O}C for 18-20 hours the trays were examined for growth .The lowest concentration of the test compounds inhibiting visible growth was taken as the inhibition value. It was confirmed that the solvent had no antimicrobial activity against any of the test organism's .The zone of inhibition was measured in mm .The results are given in Table 2.

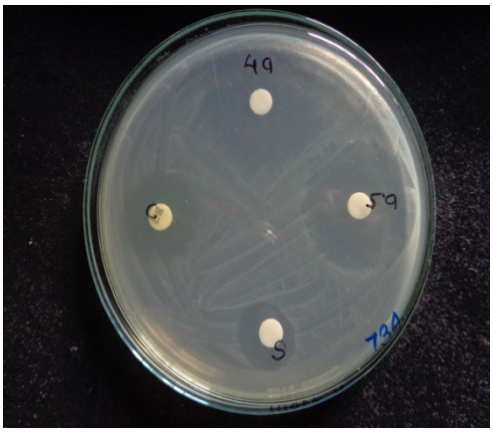
Table 2: Antibacterial activity of 2-(Substituted phenyl)-4-(4-methoxyphenyl)-5-phenyl-1H-imidazoles

Entry	**Zone of inhibition in mm**			
	Bacteria			
	K P	***E C***	***S A***	***S T***	***P A***
4a	20	16	38	11
26				
4b	10	12	26	14
21				
4c	15	19	12	17
26				
4d	22	NF	19	13
14				
4e	20	NF	08	12
19				
4f	13	22	15	09
12				
4g	08	14	19	06
17				
4h	NF	NF	21	
18	17			
4i	29	10	13	NF
13				
4j	29	NF	12	04
09				
4k	NF	17	19	NF
17				
4l	12	09	17	16
NF				

Tetracycline 33	21	36	32	35
K P=K. pneumonia, E C= E. coli, S A= S. aureus , S T= S. typhi , P A= P. aerugonosa . Control: Dimethylformamide(DMF) , NF-Not Found .				



Klebsellia pneumonia



Escherichia coli

Conclusion

In the current study a series of 12 different 2-(substituted phenyl)-4-(4-methoxyphenyl)-5-phenyl-1H-imidazole derivatives were synthesized and evaluated for their antibacterial activity against gram – positive and gram- negative bacterial strain. We have developed a mild, convenient method for the synthesis of substituted -1H- imidazole by using 4,4'-dimethoxybenzil , ammonium acetate and substituted aromatic aldehyde in glacial acetic acid . The excellent yield, easy work-up and simple reaction procedure is highlighted in the present work. Among the tested compounds 4a, 4b, 4f, 4i and 4j were found to be more potent antibacterial drugs. It can be concluded that 2-(Substituted phenyl)-4-(4-methoxyphenyl)-5phenyl-1H-imidazoles can act as a template for further development through modification to design more potent biologically active compounds.

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References

[1] Renukadevi P, Biradkar J.S, Hiremath S.P, Manjanath S Y, Synthesis and antimicrobial activity of 1,2-Di-substituted- 4-[5'-Substituted-2'-phenylindole-3'-yl)methylene] imidazolelin-5(4H)-one,Indian J.Heterocycle Chem 1997,6,277-280.

[2] Paul W.B, Heterocycle HIV-I protease inhibitors, Org.lett 1999,1(2),249-252 .

[3] Chengzhi Z, Sepehr.S, Edmund J. M, Sonja K, Jennifer C R , Khalid D.B, 2,4,5-Trisubstituted imidazoles novel non-toxic modulatorsof P-glycoprotein mediated multidrug resistance ,Bioorg Med Chem Lett 2000 ,10(23), 2603-2605 .

[4] Robert A.T, Charles F H, Caesar R .S, Studies on imidazole 4-methylimidazole and related compounds, J Am Chem Soc 1949, 71(8), 2801-2803.

[5] Shealy Y E, Montogomery J.A, Loster W.R, Antitumor activity of triazenoimidazoles, J.Biochem Pharmacol , 1962,11,674.

[6] Miyachi H, Kiyota H, Segawa M, Novel imidazole derivativeswith subtype selective antimuscarinic activity, Bioorg Med.chem lett, 1998, 18, 2163-2168.

[7] Sharpe T.R, Cherkovsky S.C, Hewes W.E.,Smith D.H, Preparation antiarthritic and analgesic activity of -4,5- diaryl-2-(Substituted thio)-1H-imidazole and their sulfoxide and sulfones.J.Med.Chem, 1985,28,1188-1194

[8] Ha Sircar, Bradley I, Duell James A, Bristol Ronald E, Cardiotonic agents 1,2-Dihydro-5-[4-(1H-imidazol-1- yl)phenyl-6-methyl-2-oxo-3-pyridine cardio tonic and related compound synthesis and isotropic activity , J.Med.chem ,1987,30,1023-1029.

[9] Wang I, Woods K.W, Li Q, Barr K.J, Mecroskey R.W, Hannick S.M, Gherke L, Orally active heteocycle-based combretastatinA-4analogues synthesis structural activity relationship and antitumor activity evaluation .J.Med Chem, 2002,45,1697-1711.

[10] Siddiqui S.A, Narkhede U.C, Palimkar S.S, Daniel T, Lahoti R.J, Rapid synthesis of 2,4,5-triaryl imidazoles from aryl aldehyes and 1,2-diketone,Tetrahedron 2005, 61, 3539-3546.

[11] Mohammadi A A, Mivechi M, Kefayati H , Potassium aluminum sulfate (Alum) an efficient catalyst for the one pot synthesis of trisubstituted imidazoles ,Monatsh Chem ,2008,139 , 935-937.

[12] Mohammed A.F, Kokare N.D, Sangshetti J.N, Shinde D.B, Sulfanilic acid catalysed facile one-pot synthesis of 2,4,5-triarylimidazolesfrom Benzil/ Benzoin and aromatic aldehydes .J.Korean Chem Soc ,2007 , 51 , 418-422.

[13] Liu J, Chem J, Zhao J, Zhao Y, LiL , Zhang H, A modified procedure for the synthesis of 1-arylimidazoles synthesis 2003,17,2661-2266.

[14] Sangshetti J.N, Kokare N.D, Kotharkara S.A , Shinde D.B, A new synthesis of 4-Substituted 3H1,2,3,5- oxathiadiazole -2-oxide bearing 1,2 , JChem sci ,2008,120(5) , 463-467.

[15] Parveen A , Ahmed M.D, Rafi S.K, Shaikh K.A , Deshmukh S.P, Pawar R.P, Efficient synthesis of 2,4,5-triaryl substituted imidazoles under solvent free conditions at room temperature Arkivoc , 2007, 12-18.

[16] Sharma S D, Hazarika P, Konwar D, An efficient and one pot synthesis of 2,4,5-trisubstitutedand 1,2,4,5- tetrasubstituted imidazoles catalysed by InCl3.3H2O, Tetrahedron Lett 2008, 49,2216-2220.

[17] Kidwai M, Saxena S, RAstogi R, Rastogi S, An efficient synthesis of 2,4,5-trisubstituted and 1,2,4,5- tetrasubstituted-1H-imidazoles ,Bull Korean Chem Soc, 2005, 26(12), 2051-2053.

[18] Lidsrom P, Tierney J, wathey B, Westman J, Microwave assisted organic synthesis - a review, Tetrahedron, 2001 , 57, 9225.