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Simple grinding, one pot, three component synthesis of substituted imidazoles using potassium dihydrogen phosphate and their antifungal screening

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Abstract
An efficient, one pot, three component solvent free synthesis of substituted imidazoles has been done with the help of reaction between substituted benzaldehyde, benzil and ammonium acetate in the presence of potassium dihydrogen phosphate by grinding method. The notable advantage of grinding method are the good yields, easy workup, short time reaction and environmentally benign as compared to conventional method. The synthesized compounds have been screened for their antifungal activity against *Asperillus niger* and Rhizoctonia solani. These synthesized compounds were characterized by IR, ^{1}HNMR and melting point.

Keywords: Imidazoles, solvent free, grinding, synthesis and antifungal activity

1. Introduction
Imidazole derivatives are a very important class of heterocyclic compounds because they are found in many pharmacologically active compounds and natural products. Thus the development of a greener method for the synthesis of substituted imidazoles would be highly desirable. Potassium dihydrogen phosphate used as a buffer neutralizing agent and has been found as a moderate and effective catalyst in the synthesis of imidazole derivatives.
Some of the Imidazole derivatives are known as inhibitors of p38 MAP kinase, fungicides and plant growth regulators [1-4]. Imidazoles are made up of planar five membered ring system with three carbon and two nitrogen atoms at first and third positions. Imidazole is also known as 1,3-diaza-2,4-cyclopentadiene. Imidazole and its derivatives contain a broad spectrum of different types of pharmacological and agrochemical properties such as antibacterial [5, 6], anticancer [7], anti-depressant [8], anticoagulants [9], anti-inflammatory [10], antifungal [11], antiviral and antitubercular [12-13], antimalarial and antidiabetic [14] etc.
Imidazoles are also known as diazole having non adjacent nitrogen atom. Many natural products, biologically active synthetic compounds and nucleic acids contain imidazole ring [15]. Some of imidazole derivatives have found application as fluorescent whitening agents.

2. Materials and Methods
2.1. Experimental section
2.1.1 Method A (Conventional)
A mixture of substituted benzaldehyde, benzil, ammonium acetate in methanol was taken in a flask. Potassium dihydrogen phosphate (10mol%) was added as a catalyst. The reaction mixture was refluxed at 80 °C for 3 hours and left overnight at room temperature. Progress of the reaction was monitored with the help of thin layer chromatography. After completion of the reaction, the reaction mixture was cooled and then recrystallized from ethylacetate and the final product was obtained.

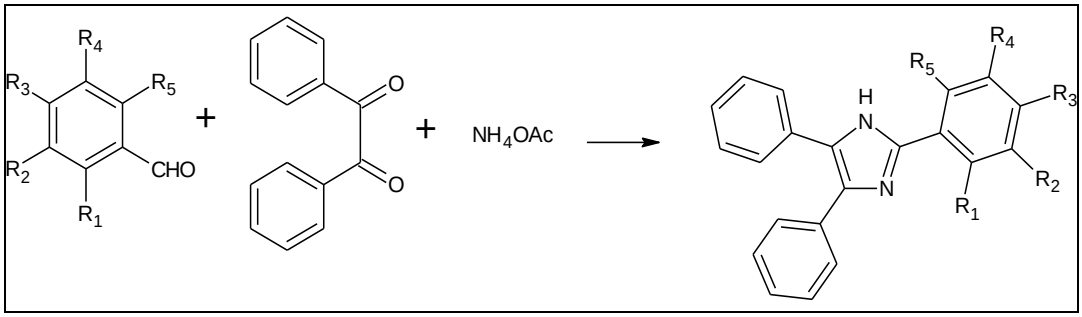
2.1.2 Method B (Grinding)
A mixture of substituted benzaldehyde, benzil, ammonium acetate and KH_2PO_4 (10mol%) were ground together in a mortar with a pestle at room temperature for 15 minutes and the reaction mixture was left overnight at room temperature. The completion of reaction was confirmed by thin layer chromatography and then the reaction mixture was poured over crushed ice and the solid that separated out was filtered, washed with water and dried. It was crystallized from ethylacetate to afford **c**ompound.

3. Result

Scheme 3.1. Synthesis of 2-(-3,4,5-trimethoxy phenyl)-/2-(2-hydroxy phenyl) -/2-(3-hydroxy phenyl) - /2-(2-chloro phenyl) -/2-(4-methyl phenyl)-4,5-diphenyl-1H-imidazole (8-12) by conventional and grinding method.

Method: (Conventional/grinding method)

3,4,5-trimethoxy benzaldehyde (1), 2-hydroxy benzaldehyde (2), 3-hydroxy benzaldehyde (3), 2-chloro benzaldehyde (4), 4-methyl benzaldehyde (5), benzil (6) and ammonium acetate (7) react with 10 mol% potassium dihydrogen phosphate in equimolar ratio in a flask with constant stirring (in presence of solvent)/grinding (without solvent) gives 2-(-3,4,5-trimethoxy phenyl)- 4,5-diphenyl-1H-imidazole (8), 2-(2-hydroxy phenyl) - 4,5-diphenyl-1H-imidazole (9), 2-(3-hydroxy phenyl)-4,5-diphenyl-1H-imidazole (10), 2-(2-chloro phenyl)-4,5-diphenyl-1H-imidazole (11), 2-(4-methyl phenyl) - 4,5-diphenyl-1H-imidazole (12) in good yields (scheme 3.1). Physical data of substituted-4,5-diphenyl-1H-imidazole (8-12) have been given in table 1,2 and 3.



1-5 **6** **7** **8-12**

Reagents and Reaction Conditions

Method A: Conventional (10 mol% KH_2PO_4, methanol), stirring

Method B: Grinding at room temperature (10 mol% KH_2PO_4)

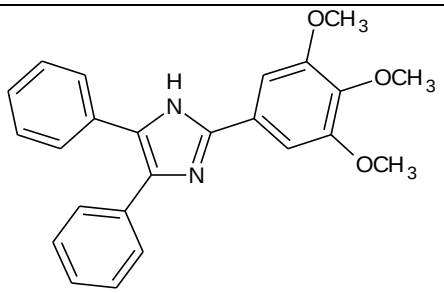
Table 1: KH_2PO_4 catalyzed synthesis of substituted imidazoles.

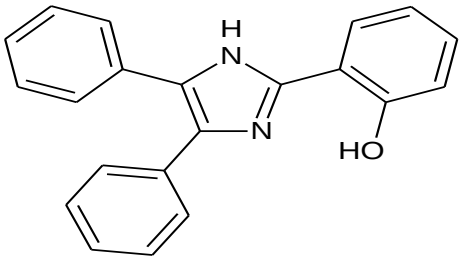
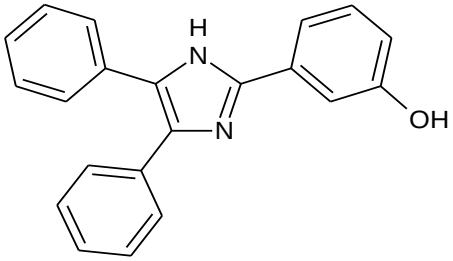
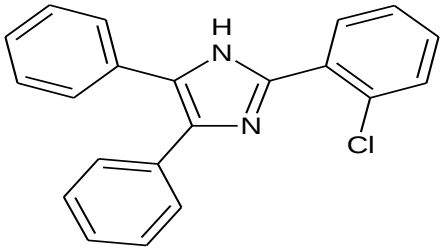
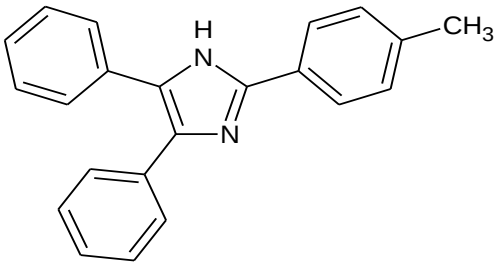
Compound Number	R_1	R_2	R_3	R_4	R_5
1,8	H	OCH_3	OCH_3	OCH_3	H
2,9	OH	H	H	H	H
3,10	H	OH	H	H	H
4,11	Cl	H	H	H	H
5,12	H	H	CH_3	H	H

Table 2: A comparative analysis of physical data of substituted imidazole (8-12) in between conventional and grinding method.

Compound Number	Conventional Method		Grinding Method	
	Time (Hours)	Yield (%)	Time (minute)	Yield (%)
8	3	78	15, Left overnight	84
9	3	82	16, Left overnight	88
10	3.5	80	15 , Left overnight	86
11	3	77	14	81
12	4	79	15	82

Table 3: Physical data of substituted imidazole (8-12) in conventional and grinding method.

Compound No.	Molecular Formula	Structure	Melting Point (°C)	
			Conventional method	Grinding method
8	$C_{24}H_{22}N_2O_3$	 2-(-3,4,5 trimethoxyphenyl)-4,5 diphenyl-1H-imidazole	252-253	251-252

9	$C_{21}H_{16}N_2O$	 2-(2-hydroxyphenyl)-4,5 diphenyl-1H-imidazole	119-20	118-120
10	$C_{21}H_{16}N_2O$	 2-(3-hydroxyphenyl)-4,5 diphenyl-1H-imidazole	130-32	129-131
11	$C_{21}H_{15}ClN_2$	 2-(2-chlorophenyl)-4,5 diphenyl-1H-imidazole	195-97	195-196
12	$C_{22}H_{18}N_2$	 2-(4-methylphenyl)-4,5 diphenyl-1H-imidazole	233-35	233-234

3.2 Spectral data of some selected compounds

2-(3,4,5-trimethoxyphenyl)-4,5-diphenyl-1H-imidazole (8)
Solid ; M. P.:252-253°C; IR (KBr) : 3318 (NH), 3066 (C=CH), 1591 (C=C, aromatic), 1450 (CN); ^{1}HNMR ($CDCl_3$):3.12 **(**s, 9H, 3×OCH_3); 7.95-7.61 (m, 2×C_6H_5, 10H); 7.50-7.46 (d, 2H); 12.62 (s, 1H, NH)

2-(2-hydroxyphenyl)-4,5-diphenyl-1H-imidazole (9)
Solid; M. P.:119-120°C (lit. m.p. 118-120°C; [16]; IR (KBr): 3315(NH), 3066 (C=CH), 1593 (C=C, aromatic), 1450 (CN), 3713 (OH); ^{1}HNMR ($CDCl_3$):7.61-7.98 (m, 2×C_6H_5, 10H); 12.02 (s, 1H, NH); 7.53-7.49 (d, 4H); 3.45 (s, 1H, OH)

2-(3-hydroxyphenyl)-4,5-diphenyl-1H-imidazole (10)
Solid; M. P.:130-132°C; IR (KBr): 3317 (NH), 3066 (C=CH), 1592 (C=C, aromatic), 1450 (CN), 3709 (OH); ^{1}HNMR ($CDCl_3$):7.70-7.98 (m, 2×C_6H_5, 10H); 12.01 (s, 1H, NH); 7.48-7.50 (m, 4H); 3.44 (s, 1H, OH)

4. Bioevaluation

The synthesized compounds have been screened for their antifungal activity against *Rhizoctonia solani* and *Aspergillus niger* fungi by Poisoned Food Techniques [17] at 50, 100, 150 and 200µg/ml concentrations. The degree of inhibition of growth was calculated from the mean differences between treatments and the control or percentage of latter by using the formula mentioned below. The data are presented in table 4.

$$\% \text{ inhibition} = \frac{C-T}{C} \times 100$$

Where

C = mycelial growth in control dish
T = mycelial growth in treated dish

Table 4: Antifungal activity of various substituted imidazole (8-12)

Compound no.	% age growth inhibition								*Rhizoctonia solani*	*Aspergillus niger*
	Fungi									
	Rhizoctoni solani (Conc.)µg/ml				*Aspergillus niger* (Conc.)µg/ml				EC_{50} µg/ml	EC_{50} µg/ml
	50	100	150	200	50	100	150	200		
8	42.85	50	57.14	71.42	A	a	31	47	100.00	A
9	A	a	28	54	49.25	55.00	60.55	66.23	192.31	56.52
10	28.57	35.71	57.14	64.28	26.35	33.00	39.25	48.00	133.35	188.58
11	35.71	51.42	57.14	58.57	37.00	45.58	53.58	62.88	83.35	127.63
12	A	a	36	52	30.25	39.02	46.74	55.00	193.75	169.74

a: no growth inhibition

5. Discussion

Following our methods in the synthesis of substituted imidazoles, we have decided the grinding technique is better after the comparison has been done in between conventional and grinding method. Because grinding method is environmentally benign, easy to handle and short time reaction. These synthesized compounds represent a great example of antifungal compounds.

Perusal of activity data delineated in figure 1 showed that compound 2-(2-chlorophenyl)-4,5-diphenyl-1H-imidazole (11) showed the percentage growth inhibition 35.71, 51.42, 57.14 and 58.57% at 50, 100, 150 and 200µg/ml respectively against the tested fungi *Rhizoctonia solani*. This compound was found most active as compared to other compounds in this series with 83.35µg/ml EC_{50} value.

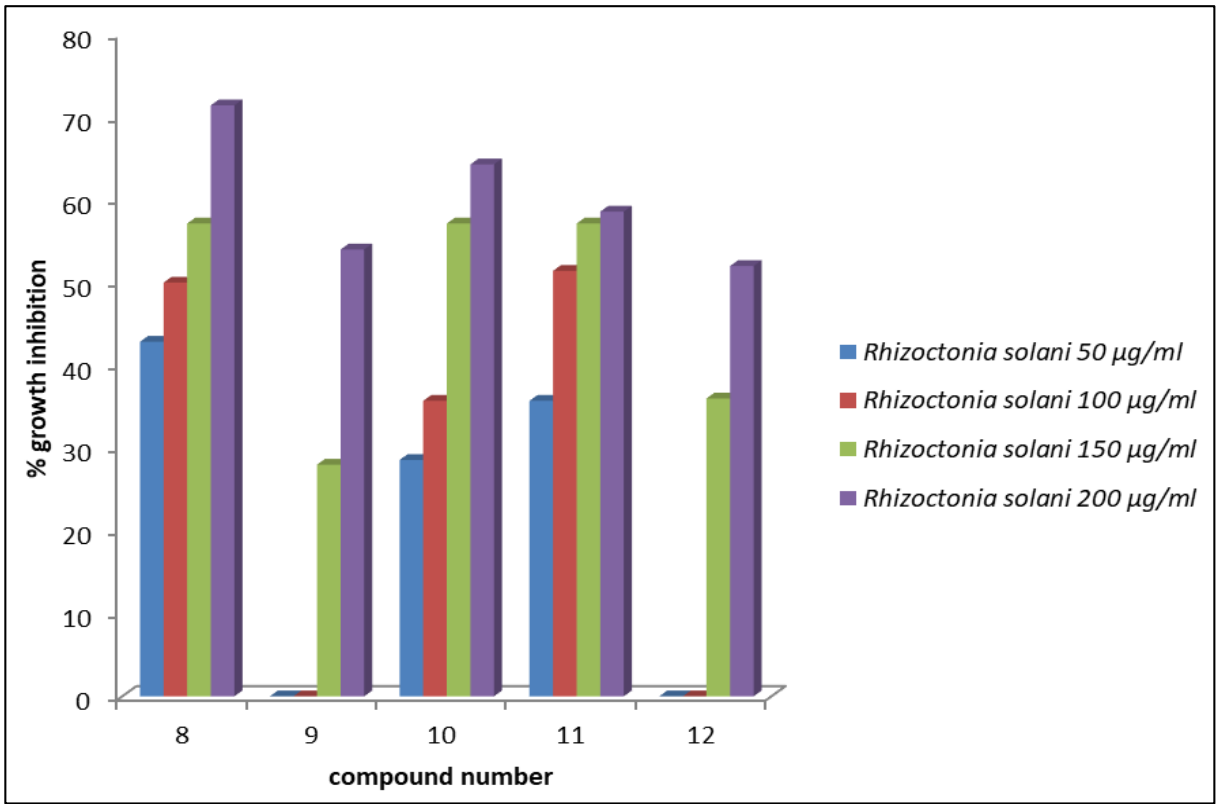


Fig 1: Antifungal activity of substituted imidazoles (8-12) against *Rhizoctonia solani*

As outlined in figure 2, compound 2-(2-hydroxyphenyl)-4,5-diphenyl-1H-imidazole (9) was found most active in this series with 56.52µg/ml EC_{50} value as compared to other compounds. This compound has shown 49.25, 55.00, 60.55 and 66.23% growth inhibition at all the tested concentrations i.e. 50 µg/ml, 100 µg/ml, 150 µg/ml and 200µg/ml respectively against *Aspergillus niger* fungus.

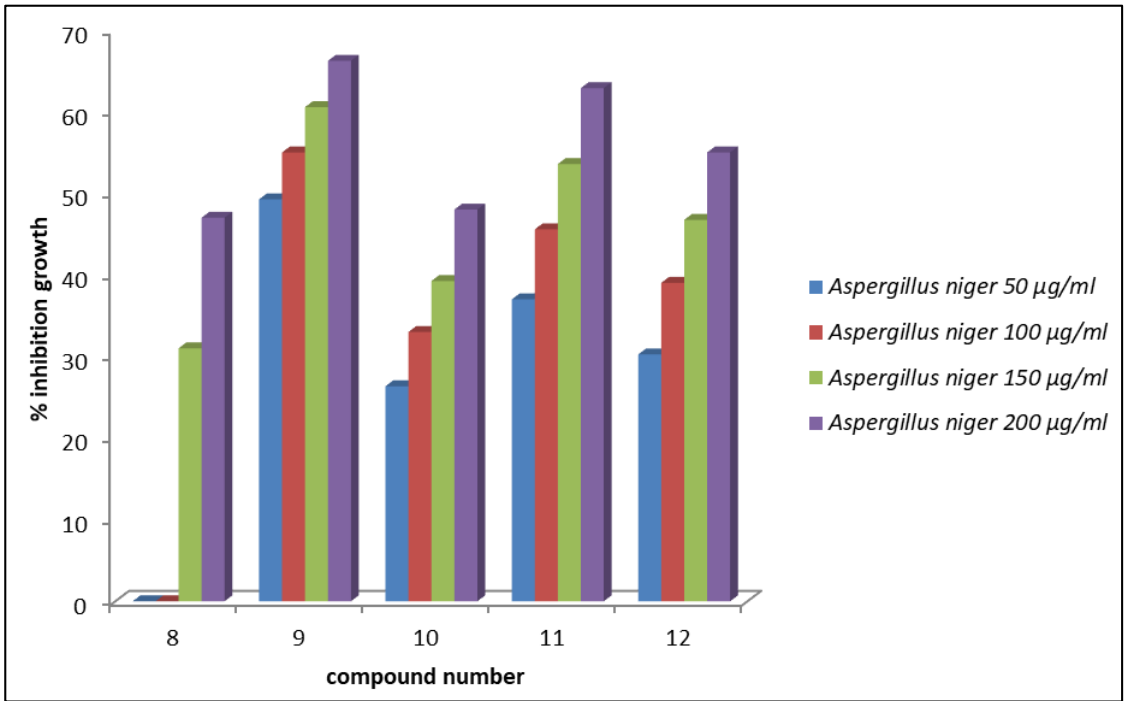


Fig 2: Antifungal activity of substituted imidazoles (8-12) against *Aspergillus niger*

6. Conclusion

We have synthesized some novel substituted imidazoles by grinding methods which is environmentally benign, solvent free and give good yields as compared to conventional method. Potassium dihydrogen phosphate has been found as a effective catalyst for one pot condensation of benzil, ammonium acetate and substituted benzaldehydes.These compounds have been screened for their antifungal activity against *Aspergillus niger* and *Rhizoctonia solani* fungi.

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