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Waste Curd Water catalyzed synthesis of 1, 2, 4-triazole derivatives and evaluation of their antifungal activity

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Abstract

A series of 1,2,4-triazole derivative having different substituent were synthesized with starting material aromatic aldehyde, methyl phenyl thiocarbazide and 4-chloro-2nitro aniline in presence of waste curd water (WCW) under microwave irradiation. Synthesized compounds were characterized by elemental analysis, IR, ^{1}HNMR spectroscopy. The antifungal activity of synthesized compounds was tested. Observation indicates that some 1,2,4-triazole derivative exhibit good antifungal activity against two fungus species.

Key words:- 1,2,4-triazole, microwave assistant synthesis, antifungal activity, waste curd water.

Introduction

1,2,4-triazole is a part of 5-membered heterocyclic family. 1,2,4-triazole ring consist of three nitrogen two carbon atom. Triazole exhibit significant biological and pharmacological activities such a antibacterial[1], antifungal[2], antiviral[3], antiinflammatory[4], analgesic[5], antitumor[6], antitubercular, antimalarial, antimigrane, potassium channel activators[7], anticonvulsant[8], anticancer[9], hypoglycamic[10], antidepressant[11], antiproliferation[12] and antioxidant[13]. 1,2,4-triazole ring can be considered a bioisostere of an imide, ester or carboxyl groups. Microwave assisted technique is a eco-friendly method for synthesis of 1,2,4-triazole[14]. The triazole ring exists in two isometric forms such as 1,2,3-triazole and the 1,2,4-triazole.

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1, 2, 4-triazole

1, 2, 3-triazole

Out of these isomers, 1,2,4-triazole is more potential isomers.

1,2,4-triazole derivatives are more stable compounds which showed broad range of biological activities such as antifungal, antibacterial, antiviral etc. active group of triazole damage spores of fungus and inhibit growth of fungus filament. The inhibitory activity of triazole might be due to Azoles linked to the iron which causing a blocked of the fungal ergosterol biosynthesis pathway.

Aly et al [15] synthesized 1,2,4,-triazole derivative from benzamidrazones and phthaloyl chloride in the presence of two equivalent triethylamine. With Einhorn-Brunner reaction Atkinsor et al.[16] has synthesized 1,2,4-trizole condensation of hydrazines or non-substituted hydrazine's and dicyclomines in the presence of mild acid at 140^{o}C. F.Zhao et al[17] had synthesized 1,2,4-triazole derivatives through intra-muscular rearrangement of N^{1}-nitro-2-hydrocarbylidene-hydrazine carboximidamides. Vivek K et al[18] synthesized lemon juice catalyst green synthesis of triazol based Schiff base which carried out in solvent free condition through mechanochemical study method. Jagtap et al.[19] had reported synthesis of biginelli products as a greener product using waste curd water.

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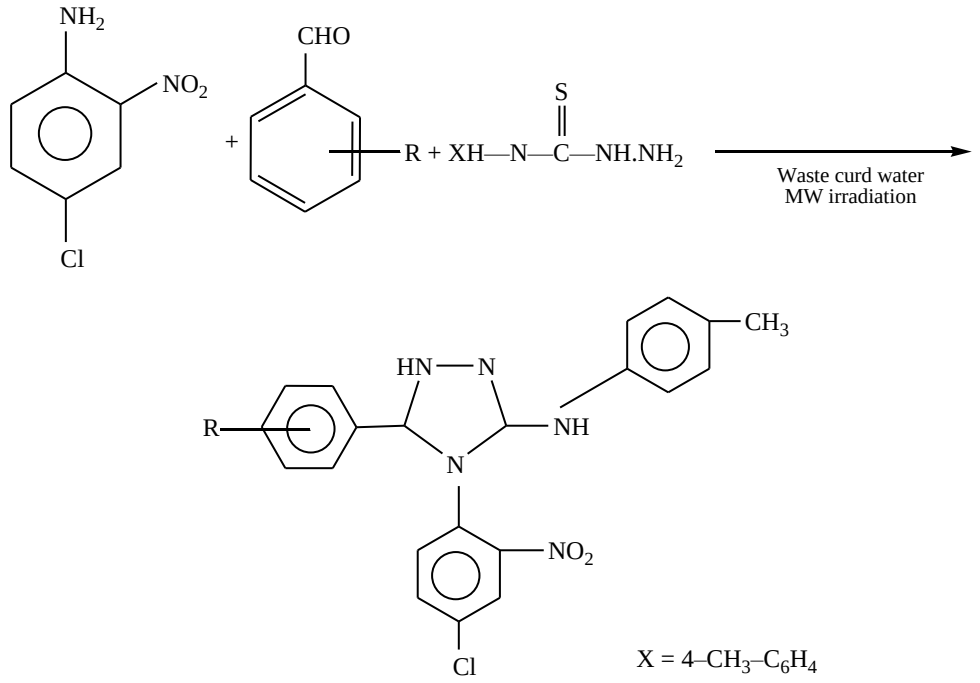
Experimental

We have developed highly efficient procedure for the synthesis of 1,2,4-triazole derivative using water containing waste curd. 4-chloro-2-nitroaniline and aromatic aldehyde when irradiated with thiosemicarbazide in presence of 10ml WCW (Waste curd Water) yielding triazole derivatives in high yields and short reaction times.



Chemical and Apparatus

All reagents and solvents were obtained from local supplier and used without further purification. Melting point was determined on a Toshniwal apparatus. IR, 1H NMR spectra of synthesized compounds have been carried out from Deptt. of Chemistry, BHU, Varanasi. ^{1}H NMR spectra were recorded on Bruker Avance H 400 NMR spectrometer using DMSO d_6 and $CDCl_3$ as solvent and TMS as internal reference standard. The purity of compounds was check on TLC (Silica gel G) in various non-aqueous solvent system.

Preparation of Catalyst (Waste curd water)

The curd was prepared in the laboratory using the ± % of lactic acid bacteria starter culture in 100 ml pasteurized warm milk in aseptic condition and incubated at 37ºC for 48hr for activation of the culture to set the curd[27]. The water from the freshly prepared curd was removed with a muslin cloth & turbid liquid was collected. The turbid liquor was centrifuged at 4000 rpm for 15 min & filtered to collect the liquor using ordinary whatman paper. This pale-yellow 4-5 days old colored liquid (pH = 4.0) was used in the synthesis as acid catalyst cum solvent.

General procedure for synthesis of 1,2,4-triazole derivative

An equimolar mixture of substituted aromatic aldehyde (0.01 mol) 4-chloro-2-nitro-aniline (0.01 mol) and methyl phenyl thiosemicarbazide in 10ml WCW containing 1.5ml ethanol was mixed in conical flask and kept in MW 450w for irradiation. After completion of reaction, mixture was cooled at room temperature and solid mass was filtered and recrystallized from ethanol.

Here is the reported comparative study of reaction time and yield in synthesis of 1,2,4-triazole derivatives using fruit juices and WCW as catalyst under different conditions (Table-1).

Antifungal activity

Antifungal activity of compounds 1-10 against Pythium ultimum Trow, Phytophthora infestans (Mont.) de Bary, Corynespora cassiicola, Botrytis cinerea and Rhizoctonia solani were evaluated[21]. A potted plant test method was adopted. Germination was conducted by soaking cucumber seeds in water for 2 h at 50 °C and then keeping the seeds moist for 24 h at

28 °C in an incubator. When the radicals were 0.5 cm, the seeds were grown in plastic pots containing a 1:1 (v/v) mixture of vermiculite and peat. Cucumber plants used for inoculations were at the stage of two cotyledons, and tomato plants were five cuphyllas. Tested compounds and commercial fungicides were sprayed with a hand sprayer on the surface of the leaves and on a fine morning, at the standard concentration of 100 μg/mL, and each plant was sprayed compounds and commercial fungicides 200 μL. Dimethomorph, Chlorothalonil, Validamycin, Zhongshengmycin were used as a control. After 2 h, inoculations of Phytophthora infestans, Corynespora cassiicola and Botrytis cinerea were carried out by spraying fungal spore suspension with 1×10^4 spore/ml, inoculation of Rhizoctonia solani and Pythium ultimum were carried out by spraying mycelia suspension of 2×10^4 CFU/ml, which was smashed with IKA T10 basic ULTRA-TURRAX® (Guangzhou, China). Each kind of inoculum was sprayed 300 μL/plant. Each treatment was replicated 4 times. After inoculation, the plants were maintained at 18-30 °C (mean temperature of 24 °C and above 80 % relative humidity (RH)). The antifungal activities were evaluated when the non-treated plant (blank) fully developed symptoms. The area of inoculated treated leaves covered by disease symptoms was assessed and compared to that of non-treated ones to determine the average disease index. The relative control efficacy of compounds compared to the blank assay was calculated via the following equation:

$$\text{relative control efficacy (\%)} = (CK - PT)/CK \times 100\%$$

Where CK is the average disease index during the blank assay and pt is the average disease index after treatment during testing. All experiments were replicated three times.

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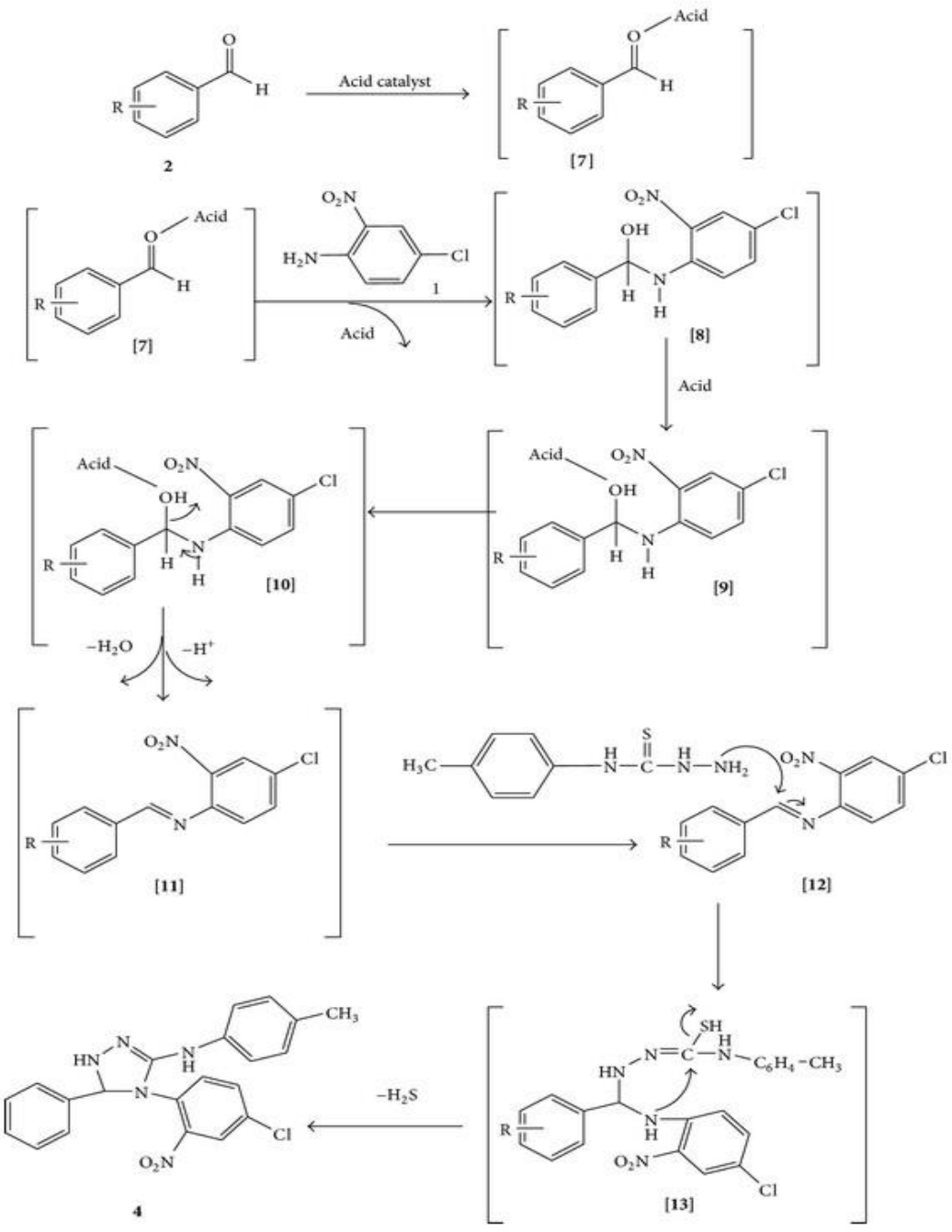
Mechanism of formation of compound



Result:- All the synthesis of compounds are previously identified by m.p., colour and elemental analysis.

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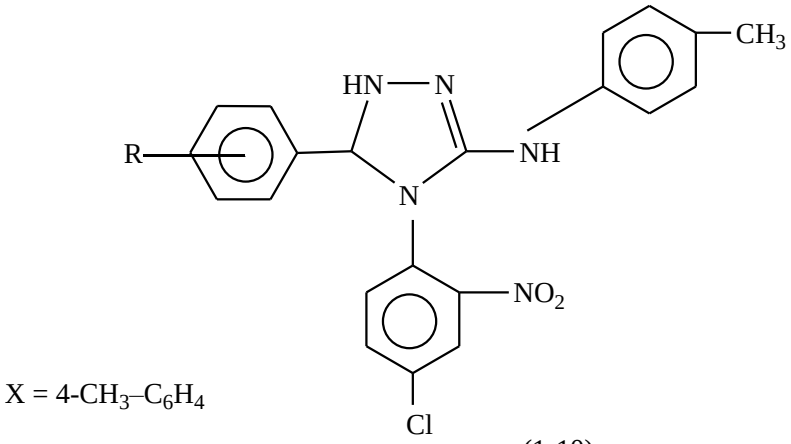
Table-1: Characterization of 1,2,4-triazole derivatives (1-10)



X = 4-CH_3–C_6H_4

(1-10)

S. No.	R	M.P.		Yield	Molecular formula	Elemental analysis				Color
		Obs. (°C)	Report. (°C)			C		N		
						Obs.	Cal.	Obs.	Cal.	
1	4–OH	191.5	190[22]	82	$C_{21}N_5O_3ClH_{15}$	60.01	59.9	16.5	16.6	Yellow
2	3–OH–4–OCH_3	221	220-222	80	$C_{25}N_5O_4ClH_{17}$	58.9	58.6	15.1	15.5	Pale Yellow
3	3,4-dimethyl	141	140[23]	81	$C_{23}N_5O_2ClH_{19}$	63.2	63.8	15.8	16.1	Orange
4	4-Cl	179	180[23]	78	$C_{21}N_5O_2Cl_2H_{14}$	57.1	57.4	15.3	15.9	Orange
5	3-OH	201	200[24]	78	$C_{21}N_5O_3ClH_{15}$	58.9	59.9	16.1	16.6	Orange
6	2, 4-dimethyl	196	195[25]	80	$C_{23}N_5O_2ClH_{19}$	64.1	63.8	16.7	16.1	Orange
7	2-OH	219	220[25]	80	$C_{21}N_5O_3ClH_{15}$	58.8	59.9	16.1	16.6	Orange
8	3-OCH_3	211	210[26]	81	$C_{22}N_5O_3ClH_{17}$	60.1	60.7	15.8	16.3	Yellow
9	4-OCH_3	241	240[26]	82	$C_{22}N_5O_3ClH_{17}$	59.9	60.7	16.6	16.3	Yellow
10	3,4-$(OCH_3)_2$	161	160[26]	83	$C_{23}N_5O_4ClH_{19}$	58.7	59.4	16.2	15.01	Orange

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Spectral study of synthesized compounds

All 10 synthesized compound were analyzed by I.R, ^{1}H NMR, ^{13}C NMR and there structure was elucidated. Obtained spectral data of synthesized compounds were co-related with literature findings. All the spectral data of compounds are mentioned in Table-2

Table-2: Spectral analysis of synthesized 1,2,4-triazole derivatives

S. No.	IUPAC name	I.R.	^{1}H NMR	^{13}CNMR
1	4-(5-tolylamino)-4-(4-chloro-2-nitrophenyl)-3,4-dihydro-2H-1,2,4-triazol-3-yl) phenol	KBr: 3475, 3354, 3165, 2982, 1583, 1365, 694cm^{-1}	(□□ppm DMSO-d_6): 2.38 (s, 3H, CH_3), 5.0 (s, 1H, OH), 5.02 (s, 1H, CH), 6.31-7.18 (m, 4H, aromatic), 6.44-6.94 (m, 4H, aromatic), 6.67-7.22 (m, 3H, aromatic), 7.01 (s, 1H, NH), 8.95 (s, 1H, NH)	400MHz, DMSO-d_6): 158.92 (C–OH), 154.92 (C=N), 140.48-125.72 (aromatic carbons), 124.06-114.20 (aromatic carbons), 132.82-113.14 (aromatic carbons), 63.92 (C–H), 23.34 (CH_3) ppm
2	4-(5-p-tolylamino)-4-(4-chloro-2-nitrophenyl)-3,4-dihydro-2H-1,2,4-triazol-3-yl)-2-methoxy phenol	3470, 3351, 3144, 2965, 1615, 1500, 1362, 1270, 1204, 1044, 702, 645cm^{-1}	(□□ppm DMSO-d_6): 2.34 (s, 3H, CH_3), 3.71 (s, 3H, OCH_3), 5.03 (s, 1H, OH), 5.06 (s, 1H, CH), 6.31-6.80 (m, 4H, aromatic), 6.40-6.53 (m, 3H, aromatic), 6.63-7.96 (m, 3H, aromatic), 7.20 (s, 1H, NH),	400MHz, DMSO-d_6): 154.55 (C–OH), 151.98 (C=N), 148.16 ($COCH_3$), 140.48-134.81 (aromatic carbons), 125.72-123.92 (aromatic carbons), 124.12-113.13 (aromatic carbons), 66.93 (C–H), 56.24 ($COCH_3$), 22.34 (CH_3) ppm

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			8.95 (s, 1H, NH)	
3	4-(4-chloro-2-nitrophenyl)-4,5 dihydro-5-(3,4-dimethylphenyl)-N-p-tolyl-1H-1,2,4-triazole-3-amine	3440, 3314, 3112, 2980, 1644, 1600, 1520, 1350, 1265, 1090, 740, 664cm^{-1}	(□□ppm DMSO-d_6): 2.24 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 5.12 (s, 1H, CH), 6.25-7.14 (m, 4H, aromatic), 6.44-6.94 (m, 3H, aromatic), 6.63-7.18 (m, 3H, aromatic), 7.13 (s, 1H, NH), 9.01 (s, 1H, NH)	400MHz, DMSO-d_6): 152.84 (C=N), 144.28-132.84 (aromatic carbons), 125.73-114.24 (aromatic carbons), 122.18-113.12 (aromatic carbons), 64.94 (C–H), 22.34 (CH_3), 17.15 (CH_3), 16.84 (CH_3) ppm
4	4-(4-chloro-2-nitrophenyl)-5-(4-chlorophenyl)-4,5-dihydro-N-p-tolyl-1H-1,2,4-triazole-3-amine	3442, 3324, 3117, 2985, 1644, 1600, 1510, 1463, 1387, 1290, 1093, 780, 640 cm^{-1}	(□□ppm DMSO-d_6): 2.32 (s, 3H, CH_3), 5.04 (s, 1H, CH), 6.33-7.12 (m, 4H, aromatic), 6.44-6.94 (m, 4H, aromatic), 6.69-7.20 (m, 3H, aromatic), 7.03 (s, 1H, NH), 8.87 (s, 1H, NH)	400MHz, DMSO-d_6): 152.92 (C=N), 147.10-133.84 (aromatic carbons), 125.78-123.22 (aromatic carbons), 114.28-111.14 (aromatic carbons), 64.93 (C–H), 24.34 (CH_3) ppm
5	3-(5-(p-tolylamino)-4-(4-chloro-2-nitro-phenyl)3,4-dihydro-2H-1,2,4-triazol-3-yl) phenol	3474, 3354, 3168, 1602, 3985, 1583, 1367, 720, 694cm^{-1}	(□□ppm DMSO-d_6): 2.32 (s, 3H, CH_3), 5.2 (s, 1H, OH), 5.02 (s, 1H, CH),	400MHz, DMSO-d_6): 155.24 (C–OH), 153.95 (C=N), 144.10-133.84 (aromatic carbons), 125.70-

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			6.33-7.12 (m, 4H, aromatic), 6.44-6.94 (m, 4H, aromatic), 6.65-7.21 (m, 3H, aromatic), 7.20 (s, 1H, NH), 9.02 (s, 1H, NH)	122.27 (aromatic carbons), 123.17-113.13 (aromatic carbons), 66.93 (C–H), 24.33 (CH_3) ppm
6	4-(4-chloro-2-nitrophenyl)-4,5 dihydro-5-(2,4-dimethylphenyl)-N-tolyl-1H-1,2,4-triazole-3-amine	3474, 3330, 3335, 3165, 3984, 1607, 1600, 1507, 1367, 1093, 720, 697cm^{-1}	(□□ppm DMSO-d_6): 2.34 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 5.07 (s, 1H, CH), 6.33-7.14 (m, 4H, aromatic), 6.44-6.94 (m, 3H, aromatic), 6.65-7.21 (m, 3H, aromatic), 7.65 (s, 1H, NH), 8.93 (s, 1H, NH)	400MHz, DMSO-d_6): 157.95 (C=N), 141.43-128.73 (aromatic carbons), 134.83-124.23 (aromatic carbons), 123.17-113.17 (aromatic carbons), 66.94 (C–H), 24.34 (CH_3), 24.14 (CH_3), 15.14 (CH_3) ppm
7	2-(5-(p-tolylamino)-4-(4-chloro-2-nitro-phenyl)3,4-dihydro-2H-1,2,4-triazol-3-yl) phenol	3474, 3353, 3157, 1633, 1500, 1340, 1200, 722, 698cm^{-1}	(□□ppm DMSO-d_6): 2.33 (s, 3H, CH_3), 5.03 (s, 1H, OH), 5.05 (s, 1H, CH), 6.33-7.17 (m, 4H, aromatic), 6.44-6.97 (m, 4H, aromatic), 6.65-7.21 (m, 3H, aromatic), 7.20 (s, 1H, NH),	400MHz, DMSO-d_6): 154.22 (C–OH), 152.91 (C=N), 140.41-133.84 (aromatic carbons), 135.33-122.12 (aromatic carbons), 127.02-113.16 (aromatic carbons), 64.93 (C–H), 24.33 (CH_3) ppm

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			8.91 (s, 1H, NH)	
8	4-(4-chloro-2-nitrophenyl)-4,5 dihydro-5-(4-dimethylphenyl)-N-tolyl-1H-1,2,4-triazole-3-amine	1253, 1202, 1153, 724, 703cm^{-1}	(□□ppm DMSO-d_6): 2.33 (s, 3H, CH_3), 3.71 (s, 3H, OCH_3), 5.03 (s, 1H, CH), 6.33-7.17 (m, 4H, aromatic), 6.44-6.97 (m, 4H, aromatic), 6.65-7.97 (m, 3H, aromatic), 7.07 (s, 1H, NH), 9.03 (s, 1H, NH)	400MHz, DMSO-d_6): 153.44 (C=N), 147.16 ($COCH_3$), 144.56-133.38 (aromatic carbons), 135.74-127.05 (aromatic carbons), 124.16-114.13 (aromatic carbons), 67.99 (C–H), 57.23 ($COCH_3$), 24.33 (CH_3) ppm
9	4-(4-chloro-2-nitrophenyl)-4,5 dihydro-5-(4-methoxyphenyl)-N-tolyl-1H-1,2,4-triazole-3-amine	3475, 3353, 2933, 1625, 1563, 1506, 1366, 1344, 1256, 1202, 1150, 725, 703cm^{-1}	(□□ppm DMSO-d_6): 2.33 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 5.05 (s, 1H, CH), 6.33-7.17 (m, 4H, aromatic), 6.62-6.95 (m, 4H, aromatic), 6.65-7.99 (m, 3H, aromatic), 7.2 (s, 1H, NH), 8.95 (s, 1H, NH)	400MHz, DMSO-d_6): 154.22 (OCH_3), 153.44 (CH_3), 149.14 ($COCH_3$) 147.64-133.38 (aromatic carbons), 135.33-124.22 (aromatic carbons), 127.22-113.17 (aromatic carbons), 67.95 (C–H), 54.92 ($COCH_3$), 55.23 (CH_3), 23.33 (CH_3) ppm
10	4-(4-chloro-2-nitrophenyl)-4,5 dihydro-5-(3,4-	3475, 3353, 2925, 1625, 1506, 1466,	(□□ppm DMSO-d_6): 2.33 (s, 3H, CH_3),	400MHz, DMSO-d_6):

	dimethoxyphenyl)-N-p-tolyl-1H-1,2,4-triazole-3-amine	1339, 1202, 1133, 1046, 796, 697cm^{-1}	3.74 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 5.03 (s, 1H, CH), 6.33-7.80 (m, 4H, aromatic), 6.45-6.94 (m, 4H, aromatic), 6.65-7.94 (m, 3H, aromatic), 7.2 (s, 1H, NH), 8.92 (s, 1H, NH)	153.94 (C=N), 152.14 (2x$COCH_3$), 148.54 (O-CH_3), 145.63 (O-CH_3) 140.47-128.74 (aromatic carbons), 123.18-121.08 (aromatic carbons), 122.27-110.13 (aromatic carbons), 65.93 (C–H), 55.23 (CH_3), 56.21 (2x$COCH_3$), 24.33 (CH_3) ppm

Antifungal activity

The antifungal activity of synthesized compound was screened against Pythium ultimum, Phytophthora infestans, Corynespora cassiicola, Botrytis cinerea, Rhizoctonia solani. Some derivative of 1,2,4-triazole showed better control efficiency against fungi Pythium ultimum at a concentration of 100µg/ml. Compound 1 inhibit growth 65.3%, compound 8 57.3% compound 2 54.4% and compound 6 11.13% which is better than control. Other compounds exhibit lower activity against Pythium ultimum such as compound 3 (-81.9%), compound 4 (-11.05%), compound 5 (-55.3%) compound 9 (-32.4%) and compound 10 (-119.6%) showed no inhibitory against Pythium ultimum. On the other hand these compounds accelerate fungal growth. The control Zhongshengmycin, Dimethomorph, Chlorothalonil, Procymidone, Validamycin cannot inhibit fungal growth.

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Table- 3: The antifungal activity of synthesized compounds in vivo at 100 ppm (%)

Compound S. no.	Pythium ultimum	Phytophthora infestans	Corynespora cassiicola	Botrytis cinerea	Rhizoctonia solani
1	65.3	-0.78	4.31	-24.30	3.85
2	54.4	-0.77	-0.89	-11.64	00
3	-8.19	-0.77	47.42	23.18	6.34
4	-11.05	-0.77	47.14	20.23	00
5	-55.3	-0.77	62.53	20.19	00
6	11.13	-0.78	49.64	-16.4	00
7	00	-o.78	40.38	-16.9	00
8	57.3	-0.58	38.14	-55.86	00
9	-32.4	0.81	24.36	-14.37	00
10	-11.96	0.43	43.57	-45.19	00
Zhongshengmycin	00	-	-	-	-
Dimethomorph	-	92.51	-	-	-
Chlorothalonil	-	-	46.41	-	-
Procymidone	-	-	-	-	61.7
Validamycin	-	-	-	-	-6.7

The compound 3,4,5 displayed excellent inhibition against other fungal Botrytis cinerea. Only compound 1 and 3 showed inhibitory action against fungi Rhizoctonia solani[27].

Conclusion

We have described that star fruit extract acting as an efficient green catalyst used for solvent free for synthesis of 2-substituted benzimidazoles under MW irradiation. In this methods have several advantages. The reaction is eco-friendly resulting high yield of product in short time.

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