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Design and synthesis of Azole containing Imidazole derivatives and evaluation of their Antifungal activity

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Abstract: Design and syntheses of some of the triazole antifungal agents having imidazole side chains, analogues to fluconazole were documented and their structures are elucidated by ^{1}H NMR and Mass spectral data. The influence of imidazole side chain moiety on in vitro antifungal activities of newly synthesized compounds were evaluated against various microorganisms such as *Aspergillus niger*, *Aspergillus fumigates* and *Candida albicans*. All the synthesized compounds showed significant activity against moulds.

Keywords: Antifungal, Triazole, Imidazole, Synthesis , Azole derivatives

Introduction:

Triazole & Imidazole are the important class of heterocyclic compounds, which have been wide scope in pharmaceutical industry because of their interesting biological activities such as antifungal and specially used in the preparation of antifungal therapy of microbes and many Triazole drugs are developed and successfully used from many years for the treatment of fungal diseases. Azoles (such as fluconazole, itraconazole, voriconazole, and posaconazole) are the important antifungal drugs for treatment of fungal diseases [1-5]. The treatment of fungal infections is problematic because of an emerging drugs resistance in fungi, therefore studies are conducted and focus on the design and synthesis of new effective antifungal compounds such as imidazole derivatives. These azoles significantly inhibit the growth of many pathogenic strains [6-9]. Various information on the synthesis and antifungal activity of structurally improved new analogues of fluconazole are known in literatures and We are focus on replacement of one of the 1,2,4-triazole ring of fluconazole with imidazole derivatives. Imidazole derivatives are

stable and shows several biological activities including antifungal, antibacterial, herbicidal [10-13].

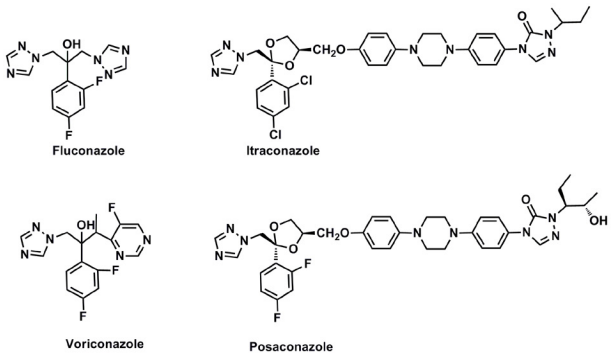


Figure 1. Triazole containing antifungal drugs used in clinical therapy

Literature precedents, revealed a pharmacophore of antifungal triazoles, which contained a triazole ring linking to a dihalophenyl ring through a two carbon chain. In addition, the carbon alpha to the phenyl ring bears a hydroxyl group (Figure-1)". We intended to alter the side chains to find potent systemic antifungal compounds with a broad antifungal spectrum and less potential to develop resistance. In our previous works, many studies on the structure-activity relationships (SAR) of antifungal azoles have been developed, and these studies have led to new compounds endowed with better biological and pharmacological properties. According to the above results, we designed a series of 1-(1*H*-1,2,4-triazole-1-yl)-2-(2,4-dichloorophenyl)-3-substituted-2-propanols containing a triazole ring, a dichlorophenyl group, a hydroxyl group and a side chain containing imidazole group. In our design, we systematically altered the structure of fluconazole as a platform and tried to insert the imidazole group into the side chain (Figure -2)".

Materials and method

All chemicals and solvents were purchased from commercial suppliers and used without further purification. The reactions and purity of the products were monitored by thin layer chromatography (TLC) using silica gel coated aluminum sheets. Mass spectra were recorded on Shimadzu mass-spectrometer. NMR spectra were recorded on a Bruker advance II 400 NMR Spectrometer.

Scheme:

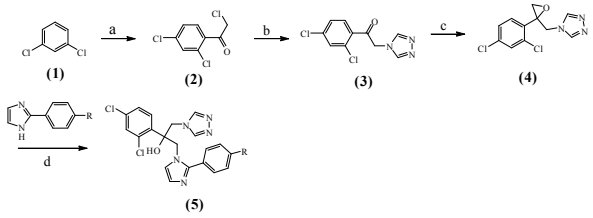


Figure 2. Structure of Azoles containing Imidazole Derivatives

Where R= H, CH_3, F, Cl , OCH_3.

Synthesis of compounds (a) $AlCl_3$, dichloromethane, chloroacetyl chloride, 25–30 °C; (b) 1,2,4-triazole, $NaHCO_3$, toluene, reflux; (c) TMSI, NaOH, toluene, 60 °C ; (d) NaH, THF, 65 °C.

Results and Discussion

Resulting compounds **(5)** were synthesize using a very efficient and straight forward synthetic route outlined in Scheme**.** Compound **(5)** was synthesized by reacting with 1,3-Dichlorobenzene, chloroacetyl chloride in presence of $AlCl_3$ as a Lewis acid and Dichloromethane as a solvent to form compound 2-Chloro-1-(2-,4-dichlorophenyl) ethanone in quantitative yield **(2)** and compound **(2)** reacted with 1,2,4 - Triazole to form compound 1-(2,4-dichlorophenyl) 2-(1-H-1,2,4-triazol-1-yl) ethanone as an intermediate (**3)** and compound **(3)** reacted with TMSI in presence of NaOH as a base and toluene as a solvent at 60^0C to form oxirane **(4) .** Target compounds **(5)** synthesized by ring-opening reaction of oxirane

(4). With substituted imidazole in presence of NaH as a base and THF as a solvent at 65^0 C . The target compounds were achieved in good yield.

General procedure for the synthesis of the derivatives 2-(2,4-Dichlorophenyl)-1-(2-Phenyl-1H-Imidazol-1-yl)-3-(4H-1,2,4-Triazol-4yl) Propan-2-ol :

2-Chloro-1-(2,4-Dichlorophenyl)-ethanone (2) :

In a clean 4 Neck RBF, take a solution of 1,3-dichlorobenzene (5.7 g, 50 mmol) in Dichlomethane (MDC, 30 ml), anhydrous aluminum chloride (7.98 g, 60 mmol) was added at 27–30 °C and stirred for 30 min. The reaction mixture was then cooled to 0-5°C and chloroacetyl chloride (6.21 g, 54 mmol) in MDC (15 ml) was added with addition funnel in 30 min at 0–5°C. After the reaction mixture was stirred at 27–30 °C for 6-7 hrs and diluted with the MDC (30 ml) and poured into 5% hydrochloric acid (50 ml) at 0–5 °C. The product was extracted with MDC (2 ×50 ml) and the combined organic layer was washed with 5% aqueous $NaHCO_3$ solution (20 ml), water (2 × 20 ml), brine (20 ml) and dried over anhydrous Na_2SO_4 and filtered. The filtrate was distilled out under reduced pressure to yield the product **2**. ^{1}H-NMR *d* (ppm): 4.65 (s, 2H); 7.49 (d, 2H); 7.82 (d, 2H) 7.65 (s, 1H). MS: *m/z* 223 (M+1).

1-(2, 4-Dichlorophenyl)-2-[1,2,4]-triazol-1-yl-ethanone (3) :

In a clean 4 Neck RBF, take a mixture of **2** (9.05 g, 47.5 mmol), 1,2,4-triazole (3.93 g,57.01 mmol), sodium bicarbonate (4.80 g, 57.00 mmol) in toluene (50 ml) was refluxed for 4-5 hrs. After the reaction was completed, the reaction mass was poured into crushed ice and extracted with toluene (2 × 50 ml). The combined organic layer was washed with H_2O (2 × 20 ml), brine (20 ml), dried over anhydrous Na_2SO_4 and filtered. The filtrate was distilled out under reduced pressure to yield compound **3** 1H-NMR *d* (ppm): 5.00 (s, 2H); 7.49 (d, 2H); 7.82 (d, 2H) 7.65 (s, 1H) , 8.06 (s, 1H) 8.41 (s, 1H) MS: *m/z* 256 (M + 1).

1-[2-(2,4-Dichlorophenyl)-oxiranylmethyl]-1H-[1,2,4]-triazole (4) :

In a clean 4 Neck RBF, take a solution of compound **3** (7.30 g, 32.70 mmol) in toluene (60 ml) in reaction mass trimethyl sulfoxonium iodide (8.64 g, 39.30 mmol) added and the 20% sodium hydroxide solution (8 ml) was also added in reaction mass. The reaction mass was heated at 60 °C for 4-5 hrs. After the reaction was completed, toluene (40 ml) was added into reaction mass to dilute it and poured into chilled water. The organic layer was washed with water (2 × 20 ml), brine (20 ml) dried over Na_2SO_4 and filtered. The filtrate was distilled out under reduced pressure to give **4** 1H-NMR *d* (ppm): 2.66–2.92 (m,2H); 4.025–4.28 (m, 2H), 7.24 (d, 2H); 7.30 (d, 2H) 7.74 (s, 1H) , 8.06 (s, 1H) 8.78 (s, 1H). MS: *m/z* 270 (M + 1).

2-(2,4-Dichlorophenyl)-1-(2-Phenyl-1H-Imidazol-1-yl)-3-(4H-1,2,4-Triazol-4yl) Propan-2-ol(5):

In a clean 4 Neck RBF, take a THF (10 ml) and added 2-(4-chlorophenyl)-2H-imidazole (**d**, 1.0 mmol) under nitrogen atmosphere, sodium hydride (1.1 mmol) was added and stirred the reaction mass for 30 min at the room temperature. After 30 min intermediate solution of 1-[2-(2,4-difluorophenyl)-oxiranyl methyl]-1*H*-[1,2,4] triazole (**4**, 1.5 mmol) in THF (15 ml) was added with the help of additional funnel dropwise into the reaction mixture at 37-40 °C, and then the reaction mass was stirred at 65 °C for 4 h. The reaction mass was cooled to room temperature and was poured into cold

water (100 ml); and extracted with ethyl acetate (2 × 100 ml). The combined organic layer was washed with water (3 × 50 ml), brine (30 ml), dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to give desired product.

1) ***$C_{20}H_{17}N_5OCl_2$*:2-(2,4-Dichlorophenyl)-1-(2-Phenyl-1H-Imidazol-1-yl)-3-(4H-1,2,4-Triazol-4yl) Propan-2-ol :** ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.28 (2H, m, $–CH_2$), 4.30 (2H, m, $–CH_2$), 6.91 (1H, d, imidazole-H), 7.23 (1H, d, imidazole-H), 7.24 (1H, m, Ar), 7.29 (1H, m, Ar), 7.41 (1H, m, Ar), 7.51 (1H, m, Ar), 7.52 (1H, m, Ar), 7.73 (1H, m, Ar), 8.28 (1H, m, Ar), 8.29 (1H, m, Ar), 8.64 (1H, m, triazole), 8.65 (1H, m, triazole), 5.52 (H, s -OH). MS: m/z 414 [M+1H]

2) ***$C_{21}H_{20}N_5OCl_2$*:2-(2,4-Dichlorophenyl)-1-(2-p-tolyl-1H-Imidazol-1-yl)-3-(4H-1,2,4-Triazol-4yl) Propan-2-ol :** ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.28 (2H, m, $–CH_2$), 4.30 (2H, m, $–CH_2$), 6.91 (1H, d, imidazole-H), 7.23 (1H, d, imidazole-H), 7.23 (1H, m, Ar), 7.28 (1H, m, Ar), 7.30 (1H, m, Ar), 7.31 (1H, m, Ar), 7.74 (1H, m, Ar), 8.51 (1H, m, Ar), 8.52 (1H, m, Ar), 8.64 (1H, m, triazole), 8.65 (1H, m, triazole), 5.52 (H, s -OH), 2.34 (H, s ,$–CH_3$). MS: m/z 428 [M+1H]

3) ***$C_{20}H_{16}N_5OCl_3$* : 1-(2-(2-Chlorophenyl)-1H-Imidazol-1-yl)-2-(2,4-Dichlorophenyl)-3-(4H-1,2,4-Triazol-4yl) Propan-2-ol :** ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.28 (2H, m, $–CH_2$), 4.30 (2H, m, $–CH_2$), 6.90 (1H, d, imidazole-H), 7.22 (1H, d, imidazole-H), 7.25 (1H, m, Ar), 7.31 (1H, m, Ar), 7.36 (1H, m, Ar), 7.40 (1H, m, Ar), 7.56 (1H, m, Ar), 7.72 (1H, m, Ar), 7.73 (1H, m, Ar), 8.64 (1H, m, triazole), 8.65 (1H, m, triazole), 5.52 (H, s -OH). MS: m/z= 448 [M+1H]

4) ***$C_{20}H_{16}N_5OCl_3$:* 1-(2-(4-Chlorophenyl)-1H-Imidazol-1-yl)-2-(2,4-Dichlorophenyl)-3-(4H-1,2,4-Triazol-4yl) Propan-2-ol :** ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.28 (2H, m, $–CH_2$), 4.30 (2H, m, $–CH_2$), 6.90 (1H, d, imidazole-H), 7.23 (1H, d, imidazole-H), 7.24 (1H, m, Ar), 7.31 (1H, m, Ar), 7.55 (1H, m, Ar), 7.56 (1H, m, Ar), 7.72 (1H, m, Ar), 8.12 (1H, m, Ar), 8.13 (1H, m, Ar), 8.64 (1H, m, triazole), 8.65 (1H, m, triazole), 5.52 (H, s -OH). MS: m/z= 448 [M+1H]

5) ***$C_{20}H_{16}N_5OCl_3$*:1-(2-(3-Chlorophenyl)-1H-Imidazol-1-yl)-2-(2,4-Dichlorophenyl)-3-(4H-1,2,4-Triazol-4yl) Propan-2-ol :** ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.28 (2H, m, $–CH_2$), 4.29 (2H, m, $–CH_2$), 6.91 (1H, d, imidazole-H), 7.21 (1H, d, imidazole-H), 7.25 (1H, m, Ar), 7.30 (1H, m, Ar), 7.45 (1H, m, Ar), 7.46 (1H, m, Ar), 7.72 (1H, m, Ar), 8.02 (1H, m, Ar), 8.17 (1H, m, Ar), 8.64 (1H, m, triazole), 8.65 (1H, m, triazole), 5.52 (H, s -OH). MS: m/z 448 [M+1H]

6) ***$C_{20}H_{16}N_5OCl_2F$* : 2-(2,4-Dichlorophenyl)-1-(2-(3-Fluorophenyl)-1H-Imidazol-1-yl)-3-(4H-1,2,4-Triazol-4yl) Propan-2-ol :** ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.29 (2H, m, $–CH_2$), 4.30 (2H, m, $–CH_2$), 6.90 (1H, d, imidazole-H), 7.22 (1H, d, imidazole-H), 7.21 (1H, m, Ar), 7.24 (1H, m, Ar), 7.31 (1H, m, Ar), 7.50 (1H, m, Ar), 7.52 (1H, m, Ar), 7.73 (1H, m, Ar), 8.06 (1H, m, Ar), 8.64 (1H, m, triazole), 8.65 (1H, m, triazole), 5.52 (H, s -OH). MS: m/z 432 [M+1H]

7) ***$C_{20}H_{16}N_5OCl_2F$* : 2-(2,4-Dichlorophenyl)-1-(2-(2-Fluorophenyl)-1H-Imidazol-1-yl)-3-(4H-1,2,4-Triazol-4yl) Propan-2-ol :** ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.28 (2H, m, $–CH_2$), 4.29 (2H, m, $–CH_2$), 6.90 (1H, d, imidazole-H), 7.23 (1H, d, imidazole-H), 7.25 (1H, m, Ar), 7.29 (1H, m, Ar), 7.30 (1H, m, Ar), 7.50 (1H, m, Ar), 7.70 (1H, m, Ar), 7.72 (1H, m, Ar), 7.78 (1H, m, Ar), 8.64 (1H, m, triazole), 8.65 (1H, m, triazole), 5.52 (H, s -OH). MS: m/z 432 [M+1H]

8) ***$C_{20}H_{16}N_5OCl_2F$* : 2-(2,4-Dichlorophenyl)-1-(2-(4-Fluorophenyl)-**

1H-Imidazol-1-yl)-3-(4H-1,2,4-Triazol-4yl) Propan-2-ol : ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.29 (2H, m, $–CH_2$), 4.30 (2H, m, $–CH_2$), 6.90 (1H, d, imidazole-H), 7.23 (1H, d, imidazole-H), 7.25 (1H, m, Ar), 7.29 (1H, m, Ar), 7.30 (1H, m, Ar), 7.30 (1H, m, Ar), 7.72 (1H, m, Ar), 7.77 (1H, m, Ar), 7.78 (1H, m, Ar), 8.64 (1H, m, triazole), 8.65 (1H, m, triazole), 5.52 (H, s -OH). MS: m/z 432 [M+1H]

9) ***$C_{21}H_{19}N_5O_2Cl_2$*: 2-(2,4-Dichlorophenyl)-1-(2-(2-Methoxyphenyl)-1H-Imidazol-1-yl)-3-(4H-1,2,4-Triazol-4yl) Propan-2-ol :** ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.28 (2H, m, $–CH_2$), 4.29 (2H, m, $–CH_2$), 6.91 (1H, d, imidazole-H), 7.23 (1H, d, imidazole-H), 7.05 (1H, m, Ar), 7.07 (1H, m, Ar), 7.25 (1H, m, Ar), 7.30 (1H, m, Ar), 7.31 (1H, m, Ar), 7.69 (1H, m, Ar), 7.72 (1H, m, Ar), 8.64 (1H, m, triazole), 8.65 (1H, m, triazole), 5.52 (H, s -OH), 3.83 (H, s ,$–CH_3$). MS: m/z 444 [M+1H]

10) ***$C_{21}H_{19}N_5O_2Cl_2$*:2-(2,4-Dichlorophenyl)-1-(2-o-tolyl-1H-Imidazol-1-yl)-3-(4H-1,2,4-Triazol-4yl) Propan-2-ol**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.28 (2H, m, $–CH_2$), 4.29 (2H, m, $–CH_2$), 6.90 (1H, d, imidazole-H), 7.23 (1H, d, imidazole-H), 7.24 (1H, m, Ar), 7.29 (1H, m, Ar), 7.29 (1H, m, Ar), 7.30 (1H, m, Ar), 7.33 (1H, m, Ar), 7.68 (1H, m, Ar), 7.74 (1H, m, Ar), 8.64 (1H, m, triazole), 8.65 (1H, m, triazole), 5.52 (H, s -OH), 3.00 (H, s ,$–CH_3$) MS: m/z 428 [M+1H]

11) ***$C_{21}H_{19}N_5OCl_2$*:2-(2,4-Dichlorophenyl)-1-(2-(4-Methoxyphenyl)-1H-Imidazol-1-yl)-3-(4H-1,2,4-Triazol-4yl) Propan-2-ol :** ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.29 (2H, m, $–CH_2$), 4.30 (2H, m, $–CH_2$), 6.90 (1H, d, imidazole-H), 7.22 (1H, d, imidazole-H), 7.05 (1H, m, Ar), 7.06 (1H, m, Ar), 7.25 (1H, m, Ar), 7.30 (1H, m, Ar), 7.73 (1H, m, Ar), 7.97 (1H, m, Ar), 7.98 (1H, m, Ar), 8.64 (1H, m, triazole), 8.65 (1H, m, triazole), 5.52 (H, s -OH), 3.84 (H, s ,$–CH_3$) MS: m/z 444 [M+1H]

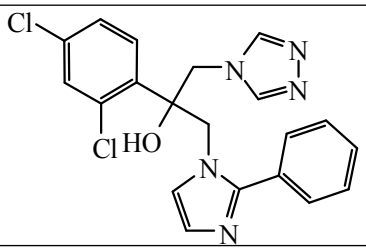
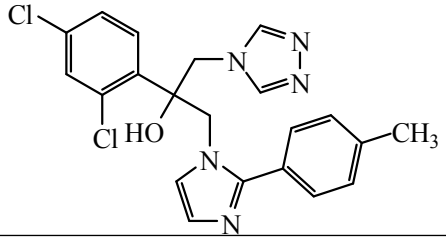
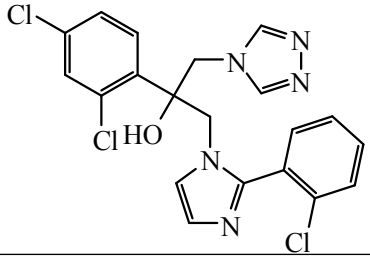
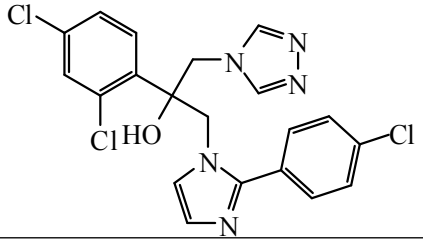
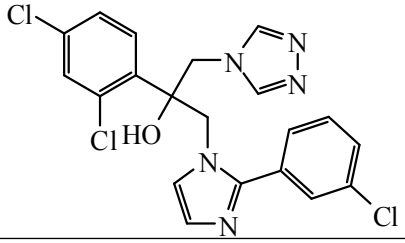
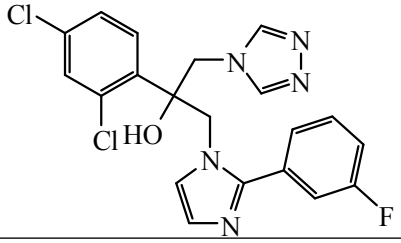
Antifungal Activity:

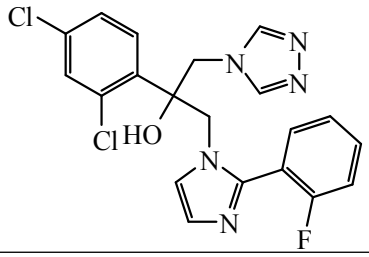
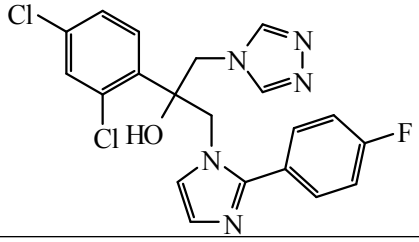
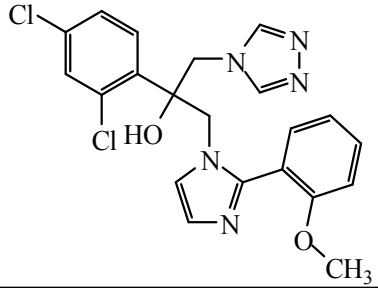
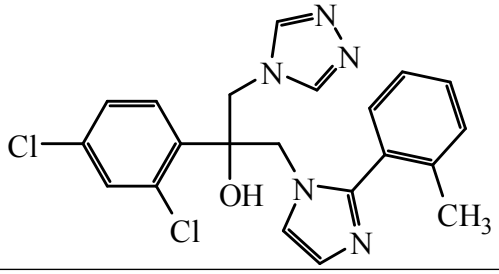
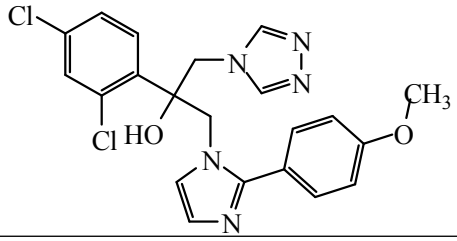
In vitro antifungal activity was determined by agar well diffusion method. Three fungal strains such as *Aspergillus niger*, *Aspergillus* fumigates and *Candida albicans* were selected for the present study. Freshly prepared sterilized potato dextrose agar media were poured 20 ml into each petri plate and allowed to solidify. The test fungal cultures were evenly spread over using sterile cotton swab. Then a well 0.5cm was made in the medium by using sterile cork borer, 50µl of the each compound were transferred into separate wells. Then these plates were incubated at 27°C for 48-96 hours. After incubation period the results were observed and measured the diameter of inhibitor zone around the each well. The zones of growth inhibition around the well were measure after 48 to 96 hours at 28°C. Nystatin was used as standard drug for antifungal activity.

Table 2: Antifungal inhibition of synthesized derivatives compounds.

SR No	Compound	C. albicans ZOI (mm)	*A. niger* ZOI (mm	A. fumigates ZOI (mm)
1	$-C_6H_5$	12	14	13
2	$4\text{-}CH_3\text{-}C_6H_4–$	15	12	14
3	$2\text{-}Cl\text{-}C_6H_4–$	17	16	16
4	$4\text{-}Cl\text{-}C_6H_4–$	20	19	18
5	$3\text{-}Cl\text{-}C_6H_4–$	19	17	13
6	$3\text{-}F\text{-}C_6H_4–$	15	18	15
7	2-F-C6H4–	16	17	19
8	$4\text{-}F\text{-}C_6H_4–$	18	19	17
9	$2\text{-}MeO\text{-}C_6H_4–$	12	14	13
10	$4\text{-}NO_2\text{-}C_6H_4–$	11	18	18
11	$4\text{-}MeO\text{-}C_6H_4–$	14	13	20
	Nystatin (Std)	24	25	22

Table 1 : Synthesized Imidazole Derivatives:

Sr. No.	R-	Product	Yield (%)
1.	-C_6H_5		82
2.	4-CH_3-C_6H_4–		80
3.	2-Cl-C_6H_4–		84
4.	4-Cl-C_6H_4–		86
5.	3-Cl-C_6H_4–		84
6.	3-F-C_6H_4–		81

7.	2-F-C6H4–		82
8.	4-F-C_6H_4–		80
9.	2-MeO-C_6H_4–		75
10.	2-CH_3-C_6H_4–		79
11.	4-MeO-C_6H_4–		73

The antifungal activities of compound (1-11) were tested against pathogenic strains such as, *Aspergillus niger, Aspergillus fumigates* and *Candida albicans* showed in Table. 2.

Compound **(4)** were shown highest zone of inhibition (20 mm) against *C. albicans* and it is better than other compound. Compound **(10)** was shown lowest activity against *C. albicans*. Compound **(4 & 8)** shown better activity than other compound against *A. niger* Figure (3).

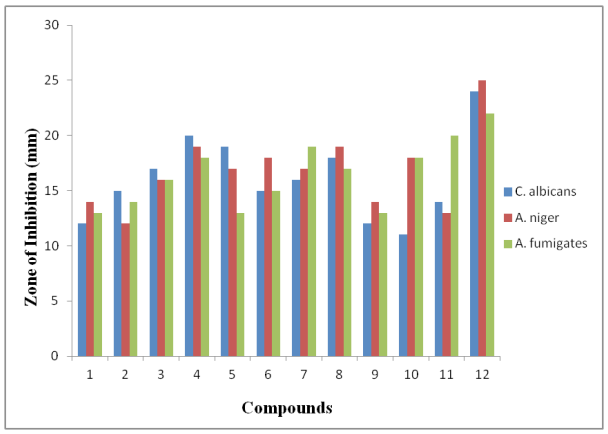


Figure 3: Antifungal activity of synthesized compound.

Conclusion:

In conclusion, we have designed and synthesized imidazole-based triazole derivatives by suitable methods. The most of the compounds showed in *vitro* antifungal activities against three fungal strains for example *Aspergillus niger*, *Aspergillus* fumigates and *Candida albicans*. The most active compound against these strains shows high valuable character for further evaluation.

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References:

1. Y. Wang, K. Xu, G. Bai, L. Huang, Q. Wu, W. Pan, S. Yu, Molecules 19, (2014) 11333-11340.
2. E. Ł. Chojnacka, J. Mierzejewska, M. M. Krawczyk, M. Bondaryk, M. Staniszewska, Bioorganic & Medicinal Chemistry 24 (2016) 6058–6065.
3. N. G. Aher, V. S. Pore, N. N. Mishra, A. Kumar, P. K. Shukla, A. Sharma, M. K. Bhat, Bioorganic & Medicinal Chemistry Letters 19 (2009) 759–763
4. R.S. Upadhayaya, S. Jain, N. Sinha, N. Kishore, R. Chandra, S. K. Arora, European Journal of Medicinal Chemistry 39 (2004) 579–592.
5. R. S. Kankate, P. S. Gide, D. P. Belsare, Arabian Journal of Chemistry (2015) xxx, xxx–xxx.
6. Gan, Lin-Ling, Fang, Bo, Zhou, Cheng-He, Bull. Korean Chem. Soc. 31 (2010) 3684-3692.
7. K. Xu, L. Huang, Z. Xu, Y. Wang, G. Bai, Q. Wu, X. Wang, S. Yu, and Y. Jiang, Drug Des Devel Ther. 9 (2015) 1459–1467.
8. J. Bartroli, E. Turmo, M. Alguero, E. Boncompte, M. L. Vericat, L. Conte, J. Ramis, M. Merlos, J. G. Rafanell, and Javier Forn J. Med. Chem. 41 (1998) 1869-1882.
9. N Lebouvier, F Pagniez, M Duflos, P Le Pape, Y. M Na, G Le Baut, M Le Borgne, Bioorg. Med. Chem. Lett. 17 (2007) 3686.
10. N.-H Nam, S Sardari, M Selecky, K Parang, Bioorg. Med. Chem. 12 (2004) 6255-6269.
11. M. M Heravi, R Motamedi, Heterocyclic. Commun. 11 (2005) 19-22.
12. J. S Park, K. A Yu, T. H Kang, S Kim, Y. G. Suh,. Bioorg. Med. Chem. Lett. 17 (2007) 3486-3490.
13. C. Sheng, W. Zhang, Curr. Med. Chem. 18 (2011) 733-66.